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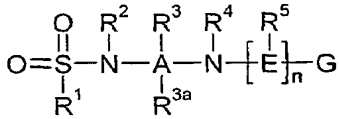

(I°)

(57) Abstract: The invention provides compounds for the prophylaxis or treatment of a disease state or condition mediated by protein kinase A or protein kinase B, the compounds having the formula (I°), or being salts or solvates thereof. In formula (I°), n is 0 or 1, A and E are alkylene 2-3 carbon atoms in length optionally substituted by R^{11} and -X-CH(R^6)(R^7); G is hydrogen when n is 0 and, when n is 1, G is hydrogen or -X-CH(R^6)(R^7); R^1 is an aryl or heteroaryl group having 5-12 ring members; R^2 and R^4 are selected from hydrogen, R^7, R^{11} and CH(R^6)(R^7); R^3, R^{3a} and R^5 are selected from hydrogen, R^{11} and -X-CH(R^6)(R^7); or any one pair or any two non-overlapping pairs selected from R^2 and R^3; R^3 and R^4; R^2 and R^5; R^3 and R^5; R^4 and R^5; R^3 and R^8; and R^4 and R^8 are linked together in a ring and together form an alkylene chain of 1-5 carbon atoms in length which may be optionally substituted by R^{11} and -X-CH(R^6)(R^7); or the pair R^2 and R^4 are linked together in a ring and together form an alkylene chain of 2-5 carbon atoms in length which may be optionally substituted by R^{11} and -X-CH(R^6)(R^7); and optionally R^3 and R^{3a} may be linked together in a ring and together form an alkylene chain of 1-6 carbon atoms in length which may be optionally substituted by R^{11} and -X-CH(R^6)(R^7); or R^6 and R^7 together with the carbon atom to which they are attached form a cyclic group having 5-12 ring members; X, R^6, R^7, R^8, R^9, R^{10} and R^{11} are each as defined in claim 1; and wherein the definitions of, A, E, G, X, n and R^1 to R^{11} are subject to the provisos set ou in claim 1.

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PHARMACEUTICAL COMPOUNDS

This invention relates to aryl- and heteroaryl-sulphonamido-diamine compounds that inhibit or modulate the activity of protein kinase A (PKA) and protein kinase B (PKB), to the use of the compounds in the treatment or prophylaxis of disease states or conditions mediated by PKA and PKB, and to novel compounds having PKA and PKB inhibitory or modulating activity. Also provided are pharmaceutical compositions containing the compounds and novel chemical intermediates.

Background of the Invention

Protein kinases constitute a large family of structurally related enzymes that are responsible for the control of a wide variety of signal transduction processes within the cell (Hardie, G. and Hanks, S. (1995) *The Protein Kinase Facts Book. I and II,* Academic Press, San Diego, CA). The kinases may be categorized into families by the substrates they phosphorylate (e.g., protein-tyrosine, protein-serine/threonine, lipids, etc.). Sequence motifs have been identified that generally correspond to each of these kinase families (e.g., Hanks, S.K., Hunter, T., *FASEB J.,* 9:576-596 (1995); Knighton, *et al., Science,* 253:407-414 (1991); Hiles, *et al., Cell,* 70:419-429 (1992); Kunz, *et al., Cell,* 73:585-596 (1993); Garcia-Bustos, *et al., EMBO J.,* 13:2352-2361 (1994)).

Protein kinases may be characterized by their regulation mechanisms. These mechanisms include, for example, autophosphorylation, transphosphorylation by other kinases, protein-protein interactions, protein-lipid interactions, and protein-polynucleotide interactions. An individual protein kinase may be regulated by more than one mechanism.

Kinases regulate many different cell processes including, but not limited to, proliferation, differentiation, apoptosis, motility, transcription, translation and other signalling processes, by adding phosphate groups to target proteins. These phosphorylation events act as molecular on/off switches that can modulate or regulate the target protein biological function. Phosphorylation of target proteins

occurs in response to a variety of extracellular signals (hormones, neurotransmitters, growth and differentiation factors, etc.), cell cycle events, environmental or nutritional stresses, etc. The appropriate protein kinase functions in signalling pathways to activate or inactivate (either directly or indirectly), for example, a metabolic enzyme, regulatory protein, receptor, cytoskeletal protein, ion channel or pump, or transcription factor. Uncontrolled signalling due to defective control of protein phosphorylation has been implicated in a number of diseases, including, for example, inflammation, cancer, allergy/asthma, disease and conditions of the immune system, disease and conditions of the central nervous system, and angiogenesis.

Apoptosis or programmed cell death is an important physiological process which removes cells no longer required by an organism. The process is important in early embryonic growth and development allowing the non-necrotic controlled breakdown, removal and recovery of cellular components. The removal of cells by apoptosis is also important in the maintenance of chromosomal and genomic integrity of growing cell populations. There are several known checkpoints in the cell growth cycle at which DNA damage and genomic integrity are carefully monitored. The response to the detection of anomalies at such checkpoints is to arrest the growth of such cells and initiate repair processes. If the damage or anomalies cannot be repaired then apoptosis is initiated by the damaged cell in order to prevent the propagation of faults and errors. Cancerous cells consistently contain numerous mutations, errors or rearrangements in their chromosomal DNA. It is widely believed that this occurs in part because the majority of tumours have a defect in one or more of the processes responsible for initiation of the apoptotic process. Normal control mechanisms cannot kill the cancerous cells and the chromosomal or DNA coding errors continue to be propagated. As a consequence restoring these pro-apoptotic signals or suppressing unregulated survival signals is an attractive means of treating cancer.

The signal transduction pathway containing the enzymes phosphatidylinositol 3-kinase (PI3K), PDK1 and PKB amongst others, has long been known to mediate

increased resistance to apoptosis or survival responses in many cells. There is a substantial amount of data to indicate that this pathway is an important survival pathway used by many growth factors to suppress apoptosis. The enzyme PI3K is activated by a range of growth and survival factors e.g. EGF, PDGF and through the generation of polyphosphatidylinositols, initiates the activation of the downstream signalling events including the activity of the kinases PDK1 and protein kinase B (PKB) also known as akt. PKB is a protein ser/thr kinase consisting of a kinase domain together with an N-terminal PH domain and C-terminal regulatory domain. The enzyme PKB itself is phosphorylated on Thr 308 by PDK1 and on Ser 473 by an as yet unidentified kinase. Full activation requires phosphorylation at both sites whilst association between PIP3 and the PH domain is required for anchoring of the enzyme to the cytoplasmic face of the lipid membrane providing optimal access to substrates.

Activated PKB in turns phosphorylates a range of substrates contributing to the overall survival response. Whilst we cannot be certain that we understand all of the factors responsible for mediating the PKB dependent survival response some important actions are believed to be phosphorylation and inactivation of the pro-apoptotic factor BAD and caspase 9, phosphorylation of Forkhead transcription factors e.g. FKHR leading to their exclusion from the nucleus, activation of the NfkappaB pathway by phosphorylation of upstream kinases in the cascade.

In addition to the anti-apoptotic and pro-survival actions of the PKB pathway, the enzyme also plays an important role in promoting cell proliferation. This action is again likely to be mediated via several actions some of which are thought to be phosphorylation and inactivation of the cyclin dependent kinase inhibitor of $p21^{Cip1/WAF1}$, and phosphorylation and activation of mTOR, a kinase controlling several aspects of cell growth.

The phosphatase PTEN which dephosphorylates and inactivates polyphosphatidyl-inositols is a key tumour suppressor protein which normally acts to regulate the PI3K/PKB survival pathway. The significance of the PI3K/PKB pathway in tumourigenesis can be judged from the observation that PTEN is one of the most

common targets of mutation in human tumours. For example in ~50% or more of melanomas (Guldberg et al 1997, Cancer Research 57, 3660-3663) and advanced prostate cancers (Cairns et al 1997 Cancer Research 57, 4997). These observations and others suggest that a wide range of tumour types are dependent on the enhanced PKB activity for growth and survival and would respond therapeutically to appropriate inhibitors of PKB.

There are 3 closely related isoforms of PKB called alpha, beta and gamma, which genetic studies suggest have distinct but overlapping functions. Evidence suggests that they can all independently play a role in cancer. For example PKB beta has been found to be over-expressed or activated in 10 – 40% of ovarian and pancreatic cancers (Bellacosa et al 1995, Int. J. Cancer 64, 280 – 285; Cheng et al 1996, PNAS 93, 3636-3641; Yuan et al 2000, Oncogene 19, 2324 – 2330), PKB alpha is amplified in human gastric, prostate and breast cancer (Staal 1987, PNAS 84, 5034 – 5037; Sun et al 2001, Am. J. Pathol. 159, 431 –437) and increased PKB gamma activity has been observed in steroid independent breast and prostate cell lines (Nakatani et al 1999, J. Biol. Chem. 274, 21528 – 21532).

The PKB pathway also functions in the growth and survival of normal tissues and may be regulated during normal physiology to control cell and tissue function. Thus disorders associated with undesirable proliferation and survival of normal cells and tissues may also benefit therapeutically from treatment with a PKB inhibitor. Examples of such disorders are disorders of immune cells associated with prolonged expansion and survival of cell population leading to a prolonged or up regulated immune response. For example, T and B lymphocyte response to cognate antigens or growth factors such as interferon gamma activates the PI3K/PKB pathway and is responsible maintaining the survival of the antigen specific lymphocyte clones during the immune response. Under conditions in which lymphocytes and other immune cells are responding to inappropriate self or foreign antigens or in which other abnormalities lead to prolonged activation, the PKB pathway contributes an important survival signal preventing the normal mechanisms by which the immune response is terminated via apoptosis of the

activated cell population. There is a considerable amount of evidence demonstrating the expansion of lymphocyte populations responding to self antigens in autoimmune conditions such as multiple sclerosis and arthritis. Expansion of lymphocyte populations responding inappropriately to foreign antigens is a feature of another set of conditions such as allergic responses, asthma etc. In summary inhibition of PKB could provide a beneficial treatment for immune disorders.

Other examples of inappropriate expansion, growth, proliferation, hyperplasia and survival of normal cells in which PKB may play a role include but are not limited to atherosclerosis, cardiac myopathy and glomerulonephritis.

In addition to the role in cell growth and survival, the PKB pathway functions in the control of glucose metabolism by insulin. Available evidence from mice deficient in the alpha and beta isoforms of PKB suggests that this action is mediated by the beta isoform. As a consequence, modulators of PKB activity may also find utility in diseases in which there is a dysfunction of glucose metabolism such as diabetes.

Cyclic AMP-dependent protein kinase (PKA) is a serine/threonine protein kinase that phosphorylates a wide range of substrates and is involved in the regulation of many cellular processes including cell growth, cell differentiation, ion-channel conductivity, gene transcription and synaptic release of neurotransmitters. In its inactive form, the PKA holoenzyme is a tetramer comprising two regulatory subunits and two catalytic subunits.

PKA acts as a link between G-protein mediated signal transduction events and the cellular processes that they regulate. Binding of a hormone ligand such as glucagon to a transmembrane receptor activates a receptor-coupled G-protein (GTP-binding and hydrolyzing protein). Upon activation, the alpha subunit of the G protein dissociates and binds to and activates adenylate cyclase, which in turn converts ATP to cyclic-AMP (cAMP). The cAMP thus produced then binds to the regulatory subunits of PKA leading to dissociation of the associated catalytic subunits. The catalytic subunits of PKA, which are inactive when associated with the regulatory

sub-units, become active upon dissociation and take part in the phosphorylation of other regulatory proteins.

For example, the catalytic sub-unit of PKA phosphorylates the kinase Phosphorylase Kinase which is involved in the phosphorylation of Phosphorylase, the enzyme responsible for breaking down glycogen to release glucose. PKA is also involved in the regulation of glucose levels by phosphorylating and deactivating glycogen synthase. Thus, PKA may be useful in the treatment or management of diseases in which there is a dysfunction of glucose metabolism such as diabetes.

PKA has also been established as an acute inhibitor of T cell activation. Anndahl *et al,* have investigated the possible role of PKA type I in HIV-induced T cell dysfunction on the basis that T cells from HIV-infected patients have increased levels of cAMP and are more sensitive to inhibition by cAMP analogues than are normal T cells. From their studies, they concluded that increased activation of PKA type I may contribute to progressive T cell dysfunction in HIV infection and that PKA type I may therefore be a potential target for immunomodulating therapy.- Aandahl, E. M., Aukrust, P., Skålhegg, B. S., Müller, F., Frøland, S. S., Hansson, V., Taskén, K. *Protein kinase A type I antagonist restores immune responses of T cells from HIV-infected patients. FASEB J.* 12, 855--862 (1998).

Because of the diversity and importance of PKA as a messenger in cell regulation, abnormal responses of cAMP leads to a variety of human diseases derived from this, such as irregular cell growth and proliferation (Stratakis, C.A.; Cho-Chung, Y.S.; Protein Kinase A and human diseases. *Trends Endrocri. Metab.* 2002, 13, 50-52). Over-expression of PKA has been observed in a variety of human cancer cells including those from ovarian, breast and colon patients. Inhibition of PKA would therefore be an approach to treatment of cancer (Li, Q.; Zhu, G-D.; *Current Topics in Medicinal Chemistry*, 2002, 2, 939-971).

For a review of the role of PKA in human disease, see for example, *Protein Kinase A and Human Disease*, Edited by Constantine A. Stratakis, Annals of the New York Academy of Sciences, Volume 968, 2002, ISBN 1-57331-412-9.

A class of isoquinolinyl-sulphonamido-diamines having PKB inhibitory activity is disclosed in WO 01/91754 (Yissum). In the compounds of WO 01/91754, the nitrogen atom of the diamine unit remote from the sulphonamide group bears an arylalkenyl group.

WO 93/13072 (Italfarmaco) discloses a class of bis-sulphonamido diamines as protein kinase inhibitors.

EP 061673, US 4,456,757, US 4,525,589 and US 4,560,755 (all to Asahi Kasei) each describe 5-isoquinolinylsulphonamido compounds as vasodilator and hypotensive agents.

GB 2248235 (Tobishi) discloses a class of aryl and heteroarylsulphonamides having smooth muscle relaxing activity.

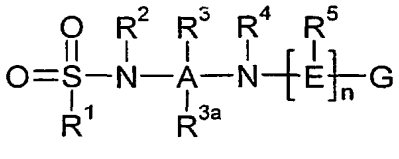
WO 93/05014 (Pharnowedropharm) discloses a class of aryl and heteroarylsulphonamides as protein kinase inhibitors but does not mention activity against protein kinases A or B.

US 4857301 (Schering) discloses antiallergic compounds having a quinolinyl or isoquinolinyl sulphonyl diamine structure.

Summary of the Invention

The invention provides compounds that have protein kinase A (PKA) and protein B (PKB) inhibiting or modulating activity, and which it is envisaged will be useful in preventing or treating disease states or conditions mediated by the PKA or PKB. Thus, for example, it is envisaged that the compounds of the invention will be useful in alleviating or reducing the incidence of cancer.

Accordingly, in a first aspect, the invention provides the use of a compound for the prophylaxis or treatment of a disease state or condition mediated by protein kinase B, the compound having the formula (I^0).



(I^0)

or a salt or solvate thereof;

wherein

n is 0 or 1;

A and E are the same or different and each is an alkylene group of 2 or 3 carbon atoms in length optionally substituted by one or more groups selected from R^{11} and –X-CH(R^6)(R^7);

G is hydrogen when n is 0 and, when n is 1, G is hydrogen or a group –X-CH(R^6)(R^7);

R^1 is an aryl or heteroaryl group having from 5 to 12 ring members;

R^2 and R^4 are the same or different and are each selected from hydrogen, R^7, R^{11} and CH(R^6)(R^7);

R^3, R^{3a} and R^5 are the same or different and are each selected from hydrogen, a group R^{11} and a group –X-CH(R^6)(R^7);

or any one pair or any two non-overlapping pairs selected from R^2 and R^3; R^3 and R^4; R^2 and R^5; R^3 and R^5; R^4 and R^5; R^3 and R^8; and R^4 and R^8 are linked together in a ring and together form an alkylene chain of 1 to 5 carbon atoms in length which may be optionally substituted by one or more groups selected from R^{11} and –X-CH(R^6)(R^7);

or the pair R^2 and R^4 are linked together in a ring and together form an alkylene chain of 2 to 5 carbon atoms in length which may be optionally substituted by one or more groups selected from R^{11} and –X-CH(R^6)(R^7);

and optionally R^3 and R^{3a} may be linked together in a ring and together form an alkylene chain of 1 to 6 carbon atoms in length which may be optionally substituted by one or more groups selected from R^{11} and –X-CH(R^6)(R^7);

X is selected from O, S, SO, SO_2 and NR^8;

R^6 and R^7 are the same or different and each is selected from hydrogen, saturated C_{1-6} hydrocarbyl, trifluoromethyl, cyano; $CONR^9R^{10}$ and aryl and heteroaryl groups having from 5 to 12 ring members; or R^6 and R^7 together with the carbon atom to which they are attached form a carbocyclic or heterocyclic group having from 5 to 12 ring members;

R^8 is selected from hydrogen, C_{1-4} hydrocarbyl, C_{1-4} acyl, C_{1-4} hydrocarbylsulphonyl;

R^9 and R^{10} are the same or different and each is selected from hydrogen and C_{1-4} hydrocarbyl; and

R^{11} is saturated C_{1-6} hydrocarbyl optionally substituted by hydroxy or C_{1-4} hydrocarbyloxy;

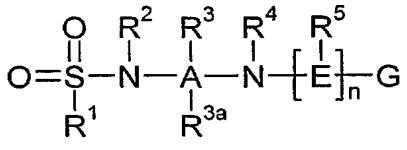
with the provisos that:

(a) when G is hydrogen and R^1 is a substituted or unsubstituted isoquinoline group, (i) at least one pair selected from R^2 and R^3; R^3 and R^4; R^2 and R^5; R^3 and R^5; and R^4 and R^5 are linked together in a ring; and/or (ii) at least one group –X-$CH(R^6)(R^7)$ is present in the compound; and/or (iii) R^3 and R^{3a} are linked together in a ring;

(b) the compound contains no more than two groups –X-$CH(R^6)(R^7)$; and

(c) when X is O, S or NR^8, a minimum chain length of two carbon atoms is interposed between X and a nitrogen atom of the moiety N-A-N.

In another aspect, the invention provides a novel compound of the formula (I):



(I)

or a salt or solvate thereof;

wherein

n is 0 or 1;

A and E are the same or different and each is an alkylene group of 2 or 3 carbon atoms in length optionally substituted by one or more groups selected from R^{11} and –X-CH(R^6)(R^7);

G is hydrogen when n is 0 and, when n is 1, G is hydrogen or a group –X-CH(R^6)(R^7);

R^1 is an aryl or heteroaryl group having from 5 to 12 ring members;

R^2 and R^4 are the same or different and are each selected from hydrogen, R^7, R^{11} and CH(R^6)(R^7);

R^3, R^{3a} and R^5 are the same or different and are each selected from hydrogen, a group R^{11} and a group –X-CH(R^6)(R^7);

or any one pair or any two non-overlapping pairs selected from R^2 and R^3; R^3 and R^4; R^2 and R^5; R^3 and R^5; R^4 and R^5; R^3 and R^8; and R^4 and R^8 are linked together in a ring and together form an alkylene chain of 1 to 5 carbon atoms in length which may be optionally substituted by one or more groups selected from R^{11} and –X-CH(R^6)(R^7);

or the pair R^2 and R^4 are linked together in a ring and together form an alkylene chain of 2 to 5 carbon atoms in length which may be optionally substituted by one or more groups selected from R^{11} and –X-CH(R^6)(R^7);

and optionally R^3 and R^{3a} may be linked together in a ring and together form an alkylene chain of 1 to 6 carbon atoms in length which may be optionally substituted by one or more groups selected from R^{11} and –X-CH(R^6)(R^7);

X is selected from O, S, SO, SO_2 and NR^8;

R^6 and R^7 are the same or different and each is selected from hydrogen, saturated C_{1-6} hydrocarbyl, trifluoromethyl, cyano; $CONR^9R^{10}$ and aryl and heteroaryl groups having from 5 to 12 ring members; or R^6 and R^7 together with the carbon atom to which they are attached form a carbocyclic or heterocyclic group having from 5 to 12 ring members;

R^8 is selected from hydrogen, C_{1-4} hydrocarbyl, C_{1-4} acyl, C_{1-4} hydrocarbylsulphonyl;

R^9 and R^{10} are the same or different and each is selected from hydrogen and C_{1-4} hydrocarbyl; and

R^{11} is saturated C_{1-6} hydrocarbyl optionally substituted by hydroxy or C_{1-4} hydrocarbyloxy;

with the provisos that:

(a) when G is hydrogen and R^1 is a substituted or unsubstituted phenyl, naphthyl or isoquinoline group, (i) at least one pair selected from R^2 and R^3; R^3 and R^4; R^2 and R^5; R^3 and R^5; and R^4 and R^5 are linked together in a ring; and/or (ii) at least one group $-X-CH(R^6)(R^7)$ is present in the compound; and/or (iii) R^3 and R^{3a} are linked together in a ring;

(b) when R^4 and R^8 are linked to form a ring, R^1 is other than an unsubstituted or substituted isoquinoline group;

(c) the compound contains no more than two groups $-X-CH(R^6)(R^7)$; and

(d) when X is O, S or NR^8, a minimum chain length of two carbon atoms is interposed between X and a nitrogen atom of the moiety N-A-N;

and excluding:

(e) compounds where, in combination, G is hydrogen, n is 1, R^4 is hydrogen, R^3 and R^5 combine to form a ring, and no group $-X-CH(R^6)(R^7)$ is present; and

(f) compounds where, in combination, G is hydrogen, n is 0, and R^3 and R^4 combine to form a ring, and no group $-X-CH(R^6)(R^7)$ is present.

In formulae (I^0) and (I), it is preferred that when G is hydrogen and R^1 is a substituted or unsubstituted isoquinoline group, (i) at least one pair selected from R^2 and R^3; R^3 and R^4; R^2 and R^5; R^3 and R^5; and R^4 and R^5 are linked together in a ring; and/or (ii) at least one group $-X-CH(R^6)(R^7)$ is present in the compound.

More preferably, when R^1 is a substituted or unsubstituted isoquinoline group, at least one group $-X-CH(R^6)(R^7)$ is present in the compound.

The invention also provides:

- A compound of the formula (I^0), (I), (II), (III), (IIIa), (IV), (IVa), (IVb), (IVc), (IVd), (V), (Va), (Vb), (Vc), (Vd), (VI), (VIa), (VIb), (VIc), (VId),

(VIe), (VIf), (VII), (VIIa), (VIII), (IX), (IXa), (Xa), (Xb), (Xc) or (Xd) and sub groups thereof as defined herein for use in the prophylaxis or treatment of a disease state or condition mediated by protein kinase A or protein kinase B.

- The use of a compound of the formula (I^0), (I), (II), (III), (IIIa), (IV), (IVa), (IVb), (IVc), (IVd), (V), (Va), (Vb), (Vc), (Vd), (VI), (VIa), (VIb), (VIc), (VId), (VIe), (VIf), (VII), (VIIa), (VIII), (IX), (IXa), (Xa), (Xb), (Xc) or (Xd) and sub groups thereof as defined herein for the manufacture of a medicament for the prophylaxis or treatment of a disease state or condition mediated by protein kinase A or protein kinase B.

- A method for the prophylaxis or treatment of a disease state or condition mediated by protein kinase A or protein kinase B, which method comprises administering to a subject in need thereof a compound of the formula (I^0), (I), (II), (III), (IIIa), (IV), (IVa), (IVb), (IVc), (IVd), (V), (Va), (Vb), (Vc), (Vd), (VI), (VIa), (VIb), (VIc), (VId), (VIe), (VIf), (VII), (VIIa), (VIII), (IX), (IXa), (Xa), (Xb), (Xc) or (Xd) and sub groups thereof as defined herein.

- A method for treating a disease or condition comprising or arising from abnormal cell growth in a mammal, which method comprises administering to the mammal a compound of the formula (I^0), (I), (II), (III), (IIIa), (IV), (IVa), (IVb), (IVc), (IVd), (V), (Va), (Vb), (Vc), (Vd), (VI), (VIa), (VIb), (VIc), (VId), (VIe), (VIf), (VII), (VIIa), (VIII), (IX), (IXa), (Xa), (Xb), (Xc) or (Xd) and sub groups thereof as defined herein in an amount effective in inhibiting abnormal cell growth.

- A method for treating a disease or condition comprising or arising from abnormal cell growth in a mammal, the method comprising administering to the mammal a compound of the formula (I^0), (I), (II), (III), (IIIa), (IV), (IVa), (IVb), (IVc), (IVd), (V), (Va), (Vb), (Vc), (Vd), (VI), (VIa), (VIb), (VIc), (VId), (VIe), (VIf), (VII), (VIIa), (VIII), (IX), (IXa), (Xa), (Xb),

(Xc) or (Xd) and sub groups thereof as defined herein as defined herein in an amount effective to inhibit protein kinase B activity.

- A method of inhibiting protein kinase A or protein kinase B, which method comprises contacting the kinase with a kinase-inhibiting compound of the formula (I^0), (I), (II), (III), (IIIa), (IV), (IVa), (IVb), (IVc), (IVd), (V), (Va), (Vb), (Vc), (Vd), (VI), (VIa), (VIb), (VIc), (VId), (VIe), (VIf), (VII), (VIIa), (VIII), (IX), (IXa), (Xa), (Xb), (Xc) or (Xd) and sub groups thereof as defined herein as defined herein.

- A method of modulating a cellular process (for example cell division) by inhibiting the activity of a protein kinase A or a protein kinase B using a compound of the formula (I^0), (I), (II), (III), (IIIa), (IV), (IVa), (IVb), (IVc), (IVd), (V), (Va), (Vb), (Vc), (Vd), (VI), (VIa), (VIb), (VIc), (VId), (VIe), (VIf), (VII), (VIIa), (VIII), (IX), (IXa), (Xa), (Xb), (Xc) or (Xd) and sub groups thereof as defined herein as defined herein.

- A method for alleviating or reducing the incidence of a disease or condition comprising or arising from abnormal cell growth in a mammal, which method comprises administering to the mammal a compound of the formula (I^0), (I), (II), (III), (IIIa), (IV), (IVa), (IVb), (IVc), (IVd), (V), (Va), (Vb), (Vc), (Vd), (VI), (VIa), (VIb), (VIc), (VId), (VIe), (VIf), (VII), (VIIa), (VIII), (IX), (IXa), (Xa), (Xb), (Xc) or (Xd) and sub groups thereof as defined herein in an amount effective in inhibiting abnormal cell growth.

- A pharmaceutical composition comprising a novel compound of the formula (I^0), (I), (II), (III), (IIIa), (IV), (IVa), (IVb), (IVc), (IVd), (V), (Va), (Vb), (Vc), (Vd), (VI), (VIa), (VIb), (VIc), (VId), (VIe), (VIf), (VII), (VIIa), (VIII), (IX), (IXa), (Xa), (Xb), (Xc) or (Xd) and sub groups thereof as defined herein and a pharmaceutically acceptable carrier.

- A compound of the formula (I^0), (I), (II), (III), (IIIa), (IV), (IVa), (IVb), (IVc), (IVd), (V), (Va), (Vb), (Vc), (Vd), (VI), (VIa), (VIb), (VIc), (VId),

(VIe), (VIf), (VII), (VIIa), (VIII), (IX), (IXa), (Xa), (Xb), (Xc) or (Xd) and sub groups thereof as defined herein for use in medicine.

- The use of a compound of the formula thereof as defined herein, for the manufacture of a medicament for the prophylaxis or treatment of any one of the disease states or conditions disclosed herein.

- A method for the treatment or prophylaxis of any one of the disease states or conditions disclosed herein, which method comprises administering to a patient (e.g. a patient in need thereof) a compound (e.g. a therapeutically effective amount) of the formula and sub-groups thereof as defined herein.

- A method for alleviating or reducing the incidence of a disease state or condition disclosed herein, which method comprises administering to a patient (e.g. a patient in need thereof) a compound (e.g. a therapeutically effective amount) of the formula and sub-groups thereof as defined herein.

In this specification, references to the formulae (I^0) and (I) shall, unless the context requires otherwise, be taken to refer also to formulae (II), (III), (IIIa), (IV), (IVa), (IVb), (IVc), (IVd), (V), (Va), (Vb), (Vc), (Vd), (VI), (VIa), (VIb), (VIc), (VId), (VIe), (VIf), (VII), (VIIa), (VIII), (IX), (IXa), (Xa), (Xb), (Xc) and (Xd) and sub groups thereof as defined herein.

In the compounds of the formula (I), G is hydrogen when n is 0 and, when n is 1, G is hydrogen or a group $-X\text{-}CH(R^6)(R^7)$.

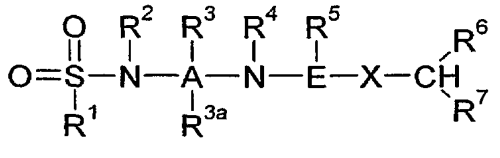
In one embodiment, at least one group $-X\text{-}CH(R^6)(R^7)$ is present.

In one group of compounds of the invention, n is 1 and G is hydrogen or a group $-X\text{-}CH(R^6)(R^7)$.

In another group of compounds of the invention, n is 0 and G is hydrogen.

Preferably the compound of the formula (I) contains no more than one group –X-CH(R^6)(R^7). Typically, the compound of the formula (I) contains a single group –X-CH(R^6)(R^7) which can be linked to the group E or the group A.

Within the general formula (I) are compounds of the formula (II):



(II)

wherein R^1, R^2, R^3, R^4, R^5, X, R^6 and R^7 are as hereinbefore defined.

The term "aryl" as used herein generally and in the context of the groups R^1, R^6 and R^7, refers to a carbocyclic group having aromatic character and the term "heteroaryl" is used herein to denote a heterocyclic group having aromatic character. The terms "aryl" and "heteroaryl" embrace polycyclic (e.g. bicyclic) ring systems wherein one or more rings are non-aromatic, provided that at least one ring is aromatic. In relation to the groups R^1, R^6 and R^7, in such polycyclic systems, the point of attachment of the polycyclic ring system to the sulphonamido or XCH-moieties will be through an aromatic ring.

The aryl or heteroaryl groups can be monocyclic or bicyclic groups and can be unsubstituted or substituted with one or more substituents, for example one or more groups R^{12} as defined below.

Examples of heteroaryl groups are monocyclic and bicyclic groups containing from five to twelve ring members, and more usually from five to ten ring members. The heteroaryl group can be, for example, a five membered or six membered monocyclic ring or a bicyclic structure formed from fused five and six membered rings or two fused six membered rings. Each ring may contain up to about four heteroatoms typically selected from nitrogen, sulphur and oxygen. Typically the heteroaryl ring will contain up to 3 heteroatoms, more usually up to 2, for example a single heteroatom. In one embodiment, the heteroaryl ring contains at least one

ring nitrogen atom. The nitrogen atoms in the heteroaryl rings can be basic, as in the case of a pyrazole, imidazole or pyridine, or essentially non-basic as in the case of an indole or pyrrole nitrogen. In general the number of basic nitrogen atoms present in the heteroaryl group, including any amino group substituents of the ring, will be less than five.

Examples of heteroaryl groups include but are not limited to those based on pyridine, pyrrole, furan, thiophene, imidazole, oxazolyl, oxadiazole, oxatriazole, isoxazole, thiazole, isothiazole, pyrazole, pyrazine, pyrimidine, pyridazine, triazine, triazole, tetrazole, quinoline, isoquinoline, benzfuran, benzthiophene, chroman, thiochroman, benzimidazole, benzoxazole, benzisoxazole, benzthiazole and benzisothiazole, isobenzofuran, isoindole, indolizine, indoline, isoindoline, purine (e.g., adenine, guanine), indazole, benzodioxole, chromene, isochromene, chroman, isochroman, benzodioxan, quinolizine, benzoxazine, benzodiazine, pyridopyridine, quinoxaline, quinazoline, cinnoline, phthalazine, naphthyridine, pyrrolopyridine, imidazopyridine, pyrrolopyrimidine, pyrazolopyridine, imidazopyrazine, imidazopyridinone, imidazopyrimidinone, isoquinolone, naphthyridinone, pyridone, pyridazinone and pteridine.

Examples of polycyclic aryl and heteroaryl groups containing an aromatic ring and a non-aromatic ring include tetrahydronaphthyl, tetrahydroisoquinolinyl, tetrahydroquinolinyl, dihydrobenzthienyl, dihydrobenzfuranyl, 2,3-dihydroisoindol-1-one, 6,7-dihydropyrrolo[3,4-b]pyrid-5-one, indolinyl and indanyl.

Examples of carbocyclic aryl groups include phenyl, naphthyl, indenyl, and tetrahydronaphthyl.

The aryl and heteroaryl groups can each be unsubstituted or substituted by one or more substituent groups R^{12} selected from halogen, hydroxy, trifluoromethyl, cyano, nitro, carboxy, amino, carbocyclic and heterocyclic groups having from 3 to 12 ring members; a group R^a-R^b wherein R^a is a bond, O, CO, $X^1C(X^2)$, $C(X^2)X^1$, $X^1C(X^2)X^1$, S, SO, SO_2, NR^c, SO_2NR^c or NR^cSO_2; and R^b is selected from hydrogen, carbocyclic and heterocyclic groups having from 3 to 7 ring members,

and a C_{1-8} hydrocarbyl group optionally substituted by one or more substituents selected from hydroxy, oxo, halogen, cyano, nitro, amino, mono- or di-C_{1-4} hydrocarbylamino, carbocyclic and heterocyclic groups having from 3 to 12 ring members and wherein one or more carbon atoms of the C_{1-8} hydrocarbyl group may optionally be replaced by O, S, SO, SO_2, NR^c, $X^1C(X^2)$, $C(X^2)X^1$ or $X^1C(X^2)X^1$;

R^c is selected from hydrogen and C_{1-4} hydrocarbyl; and

X^1 is O, S or NR^c and X^2 is =O, =S or =NR^c.

A preferred group of substituents R^{12} comprises halogen, hydroxy, trifluoromethyl, cyano, carboxy, carbocyclic and heterocyclic groups having from 3 to 12 ring members; a group R^a-R^b wherein R^a is a bond, O, CO, S, SO, SO_2; and R^b is selected from hydrogen, carbocyclic groups having from 3 to 6 ring members, heterocyclic groups having from 4 to 6 ring members, and a C_{1-8} hydrocarbyl group optionally substituted by one or more substituents selected from hydroxy, oxo, fluorine, cyano, amino, mono- or di-C_{1-4} hydrocarbylamino, carbocyclic and heterocyclic groups having from 3 to 12 ring members and wherein one or more carbon atoms of the C_{1-8} hydrocarbyl group may optionally be replaced by O, S, SO, SO_2, NR^c; and R^c is selected from hydrogen and C_{1-4} hydrocarbyl.

Where the substituent group R^{12} comprises or includes a carbocyclic or heterocyclic group, the said carbocyclic or heterocyclic group may be unsubstituted or may itself be substituted with one or more further substituent groups R^{12}. In one sub-group of compounds of the formula (I), such further substituent groups R^{12} may include carbocyclic or heterocyclic groups, which are typically not themselves further substituted. In another sub-group of compounds of the formula (I), the said further substituents do not include carbocyclic or heterocyclic groups but are otherwise selected from the groups listed above in the definition of R^{12}.

The substituents R^{10} may be selected such that they contain no more than 20 non-hydrogen atoms, for example, no more than 15 non-hydrogen atoms, e.g. no more than 12, or 11, or 10, or 9, or 8, or 7, or 6, or 5 non-hydrogen atoms.

Examples of halogen substituents include fluorine, chlorine, bromine and iodine. Fluorine and chlorine are particularly preferred.

In the definition of the compounds of the formula (I) above and as used hereinafter, the term "hydrocarbyl" is a generic term encompassing aliphatic, alicyclic and aromatic groups having an all-carbon backbone, except where otherwise stated. In certain cases, as defined herein, one or more of the carbon atoms making up the carbon backbone may be replaced by a specified atom or group of atoms. Examples of such groups include alkyl, cycloalkyl, cycloalkenyl, carbocyclic aryl, alkenyl, alkynyl, cycloalkylalkyl, cycloalkenylalkyl, and carbocyclic aralkyl, aralkenyl and aralkynyl groups. Such groups can be unsubstituted or substituted by one or more substituents as defined herein. The examples and preferences expressed below apply to each of the hydrocarbyl substituent groups or hydrocarbyl-containing substituent groups referred to in the various definitions of substituents for compounds of the formula (I) unless the context indicates otherwise.

Generally by way of example, the hydrocarbyl groups can each have up to eight carbon atoms, unless the context requires otherwise. Within the sub-set of hydrocarbyl groups having 1 to 8 carbon atoms, particular examples are C_{1-6} hydrocarbyl groups, such as C_{1-4} hydrocarbyl groups (e.g. C_{1-3} hydrocarbyl groups or C_{1-2} hydrocarbyl groups), specific examples being any individual value or combination of values selected from C_1, C_2, C_3, C_4, C_5, C_6, C_7 and C_8 hydrocarbyl groups.

The term "alkyl" covers both straight chain and branched chain alkyl groups. Examples of alkyl groups include methyl, ethyl, propyl, isopropyl, n-butyl, isobutyl, tert-butyl, n-pentyl, 2-pentyl, 3-pentyl, 2-methyl butyl, 3-methyl butyl, and n-hexyl and its isomers. Within the sub-set of alkyl groups having 1 to 8 carbon atoms, particular examples are C_{1-6} alkyl groups, such as C_{1-4} alkyl groups (e.g. C_{1-3} alkyl groups or C_{1-2} alkyl groups).

Examples of cycloalkyl groups are those derived from cyclopropane, cyclobutane, cyclopentane, cyclohexane and cycloheptane. Within the sub-set of cycloalkyl

groups the cycloalkyl group will have from 3 to 8 carbon atoms, particular examples being C_{3-6} cycloalkyl groups.

Examples of alkenyl groups include, but are not limited to, ethenyl (vinyl), 1-propenyl, 2-propenyl (allyl), isopropenyl, butenyl, buta-1,4-dienyl, pentenyl, and hexenyl. Within the sub-set of alkenyl groups the alkenyl group will have 2 to 8 carbon atoms, particular examples being C_{2-6} alkenyl groups, such as C_{2-4} alkenyl groups.

Examples of cycloalkenyl groups include, but are not limited to, cyclopropenyl, cyclobutenyl, cyclopentenyl, cyclopentadienyl and cyclohexenyl. Within the sub-set of cycloalkenyl groups the cycloalkenyl groups have from 3 to 8 carbon atoms, and particular examples are C_{3-6} cycloalkenyl groups.

Examples of alkynyl groups include, but are not limited to, ethynyl and 2-propynyl (propargyl) groups. Within the sub-set of alkynyl groups having 2 to 8 carbon atoms, particular examples are C_{2-6} alkynyl groups, such as C_{2-4} alkynyl groups.

Examples of carbocyclic aryl groups include substituted and unsubstituted phenyl.

Examples of cycloalkylalkyl, cycloalkenylalkyl, carbocyclic aralkyl, aralkenyl and aralkynyl groups include phenethyl, benzyl, styryl, phenylethynyl, cyclohexylmethyl, cyclopentylmethyl, cyclobutylmethyl, cyclopropylmethyl and cyclopentenylmethyl groups.

The definition "R^a-R^b" as used herein, either with regard to substituents present on the carbocyclic or heterocyclic moiety (e.g. as in the context of the group G), or with regard to other substituents present at other locations on the compounds of the formula (I), includes *inter alia* compounds wherein R^a is selected from a bond, O, CO, OC(O), SC(O), $NR^cC(O)$, OC(S), SC(S), $NR^cC(S)$, $OC(NR^c)$, $SC(NR^c)$, $NR^cC(NR^c)$, C(O)O, C(O)S, $C(O)NR^c$, C(S)O, C(S)S, $C(S)\,NR^c$, $C(NR^c)O$, $C(NR^c)S$, $C(NR^c)NR^c$, OC(O)O, SC(O)O, $NR^cC(O)O$, OC(S)O, SC(S)O, $NR^cC(S)O$, $OC(NR^c)O$, $SC(NR^c)O$, $NR^cC(NR^c)O$, OC(O)S, SC(O)S, $NR^cC(O)S$, OC(S)S, SC(S)S, $NR^cC(S)S$, $OC(NR^c)S$, $SC(NR^c)S$, $NR^cC(NR^c)S$, $OC(O)NR^c$,

$SC(O)NR^c$, $NR^cC(O)NR^c$, $OC(S)NR^c$, $SC(S)NR^c$, $NR^cC(S)NR^c$, $OC(NR^c)NR^c$, $SC(NR^c)NR^c$, $NR^cC(NR^c)NR^c$, S, SO, SO_2, NR^c, SO_2NR^c and NR^cSO_2 wherein R^c is as hereinbefore defined.

The moiety R^b can be hydrogen or it can be a group selected from carbocyclic and heterocyclic groups having from 3 to 12 ring members (typically 3 to 10 and more usually from 5 to 10), and a C_{1-8} hydrocarbyl group optionally substituted as hereinbefore defined.

Examples of hydrocarbyl, carbocyclic and heterocyclic groups are as set out above.

When present, the hydrocarbyl group can be substituted by one or more substituents selected from hydroxy, oxo, halogen, cyano, nitro, amino, mono- or di-C_{1-4} hydrocarbylamino, and monocyclic carbocyclic and heterocyclic groups having from 3 to 12 (typically 3 to 10 and more usually 5 to 10) ring members. Preferred substituents include halogen such as fluorine. Thus, for example, the substituent can be a partially fluorinated or perfluorinated group such as trifluoromethyl.

Where stated, one or more carbon atoms of a hydrocarbyl group may optionally be replaced by O, S, SO, SO_2, NR^c, $X^1C(X^2)$, $C(X^2)X^1$ or $X^1C(X^2)X^1$ wherein X^1 and X^2 are as hereinbefore defined, provided that at least one carbon atom of the hydrocarbyl group remains. For example, 1, 2, 3 or 4 carbon atoms of the hydrocarbyl group may be replaced by one of the atoms or groups listed, and the replacing atoms or groups may be the same or different. In general, the number of linear or backbone carbon atoms replaced will correspond to the number of linear or backbone atoms in the group replacing them. Examples of groups in which one or more carbon atom of the hydrocarbyl group have been replaced by a replacement atom or group as defined above include ethers and thioethers (C replaced by O or S), amides, esters, thioamides and thioesters (C-C replaced by $X^1C(X^2)$ or $C(X^2)X^1$), sulphones and sulphoxides (C replaced by SO or SO_2), amines (C replaced by NR^c), and ureas, carbonates and carbamates (C-C-C replaced by $X^1C(X^2)X^1$).

In the foregoing definition, when R^a is O and R^b is a C_{1-8} hydrocarbyl group, R^a and R^b together form a hydrocarbyloxy group. Preferred hydrocarbyloxy groups include saturated hydrocarbyloxy such as alkoxy (e.g. C_{1-6} alkoxy, more usually C_{1-4} alkoxy such as ethoxy and methoxy, particularly methoxy), cycloalkoxy (e.g. C_{3-6} cycloalkoxy such as cyclopropyloxy, cyclobutyloxy, cyclopentyloxy and cyclohexyloxy) and cycloalkyalkoxy (e.g. C_{3-6} cycloalkyl-C_{1-2} alkoxy such as cyclopropylmethoxy).

The hydrocarbyloxy groups can be substituted by various substituents as defined herein. For example, the alkoxy groups can be substituted by halogen (e.g. as in difluoromethoxy and trifluoromethoxy), hydroxy (e.g. as in hydroxyethoxy), C_{1-2} alkoxy (e.g. as in methoxyethoxy), hydroxy-C_{1-2} alkyl (as in hydroxyethoxyethoxy) or a cyclic group (e.g. a cycloalkyl group or non-aromatic heterocyclic group as hereinbefore defined). Examples of alkoxy groups bearing a non-aromatic heterocyclic group as a substituent are those in which the heterocyclic group is a saturated cyclic amine such as morpholine, piperidine, pyrrolidine, piperazine, C_{1-4}-alkyl-piperazines, C_{3-7}-cycloalkyl-piperazines, tetrahydropyran or tetrahydrofuran and the alkoxy group is a C_{1-4} alkoxy group, more typically a C_{1-3} alkoxy group such as methoxy, ethoxy or n-propoxy.

Alkoxy groups substituted by a monocyclic group such as pyrrolidine, piperidine, morpholine and piperazine and N-substituted derivatives thereof such as N-benzyl, N-C_{1-4} acyl and N-C_{1-4} alkoxycarbonyl. Particular examples include pyrrolidinoethoxy, piperidinoethoxy and piperazinoethoxy.

When R^a is a bond and R^b is a C_{1-8} hydrocarbyl group, examples of hydrocarbyl groups R^a-R^b are as hereinbefore defined. The hydrocarbyl groups may be saturated groups such as cycloalkyl and alkyl and particular examples of such groups include methyl, ethyl and cyclopropyl. The hydrocarbyl (e.g. alkyl) groups can be substituted by various groups and atoms as defined herein. Examples of substituted alkyl groups include alkyl groups substituted by one or more halogen atoms such as fluorine and chlorine (particular examples including bromoethyl, chloroethyl and trifluoromethyl), or hydroxy (e.g. hydroxymethyl and

hydroxyethyl), C_{1-8} acyloxy (e.g. acetoxymethyl and benzyloxymethyl), amino and mono- and dialkylamino (e.g. aminoethyl, methylaminoethyl, dimethylaminomethyl, dimethylaminoethyl and *tert*-butylaminomethyl), alkoxy (e.g. C_{1-2} alkoxy such as methoxy – as in methoxyethyl), and cyclic groups such as cycloalkyl groups, aryl groups, heteroaryl groups and non-aromatic heterocyclic groups as hereinbefore defined).

Particular examples of alkyl groups substituted by a cyclic group are those wherein the cyclic group is a saturated cyclic amine such as morpholine, piperidine, pyrrolidine, piperazine, C_{1-4}-alkyl-piperazines, C_{3-7}-cycloalkyl-piperazines, tetrahydropyran or tetrahydrofuran and the alkyl group is a C_{1-4} alkyl group, more typically a C_{1-3} alkyl group such as methyl, ethyl or n-propyl. Specific examples of alkyl groups substituted by a cyclic group include pyrrolidinomethyl, pyrrolidinopropyl, morpholinomethyl, morpholinoethyl, morpholinopropyl, piperidinylmethyl, piperazinomethyl and N-substituted forms thereof as defined herein.

Particular examples of alkyl groups substituted by aryl groups and heteroaryl groups include benzyl and pyridylmethyl groups.

When R^a is SO_2NR^c, R^b can be, for example, hydrogen or an optionally substituted C_{1-8} hydrocarbyl group, or a carbocyclic or heterocyclic group. Examples of R^a-R^b where R^a is SO_2NR^c include aminosulphonyl, C_{1-4} alkylaminosulphonyl and di-C_{1-4} alkylaminosulphonyl groups, and sulphonamides formed from a cyclic amino group such as piperidine, morpholine, pyrrolidine, or an optionally N-substituted piperazine such as N-methyl piperazine.

Examples of groups R^a-R^b where R^a is SO_2 include alkylsulphonyl, heteroarylsulphonyl and arylsulphonyl groups, particularly monocyclic aryl and heteroaryl sulphonyl groups. Particular examples include methylsulphonyl, phenylsulphonyl and toluenesulphonyl.

When R^a is NR^c, R^b can be, for example, hydrogen or an optionally substituted C_{1-8} hydrocarbyl group, or a carbocyclic or heterocyclic group. Examples of R^a-R^b where R^a is NR^c include amino, C_{1-4} alkylamino (e.g. methylamino, ethylamino, propylamino, isopropylamino, *tert*-butylamino), di-C_{1-4} alkylamino (e.g. dimethylamino and diethylamino) and cycloalkylamino (e.g. cyclopropylamino, cyclopentylamino and cyclohexylamino).

The various functional groups and substituents making up the compounds of the formula (I) are typically chosen such that the molecular weight of the compound of the formula (I) does not exceed 1000 daltons. More usually, the molecular weight of the compound will be less than 750, for example less than 700, or less than 650, or less than 600, or less than 550 daltons. More preferably, the molecular weight is less than 525 and, for example, is 500 daltons or less.

Particular examples of the aryl and heteroaryl group R^1 are set out in Table 1 below.

Table 1 -Examples of the Group R^1

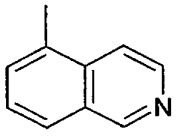
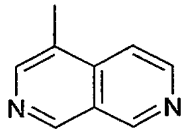
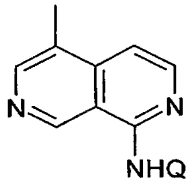
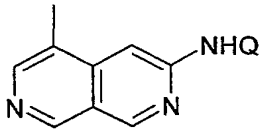
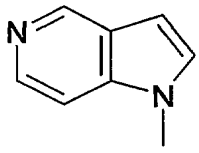
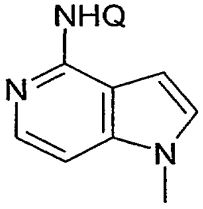
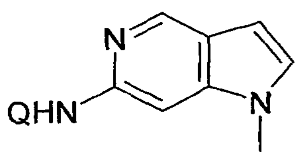
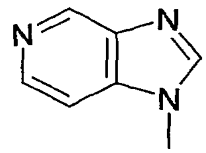
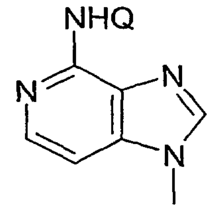
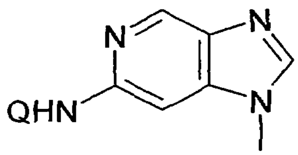
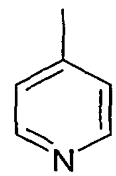
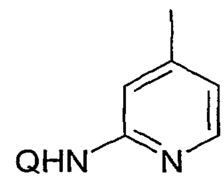
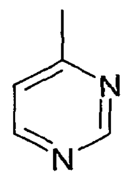
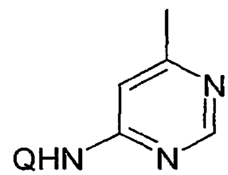
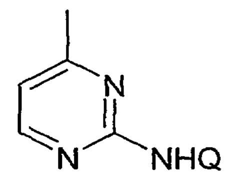
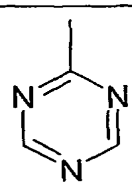
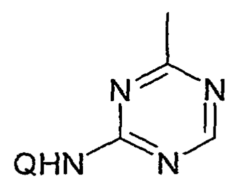
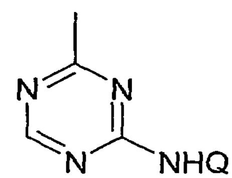
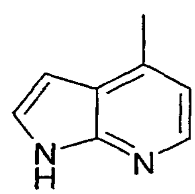
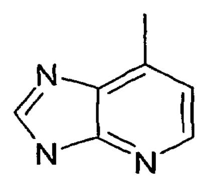
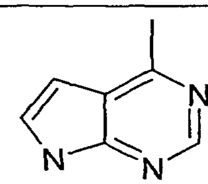
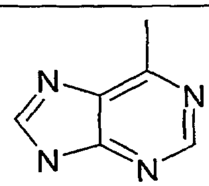
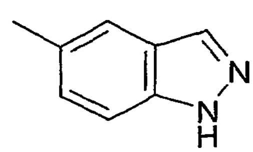
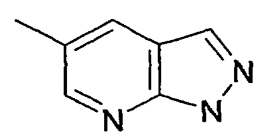
		
		

Table 1 -Examples of the Group R^1		
		
		
		
		
		
		

<u>Table 1 -Examples of the Group R[1]</u>

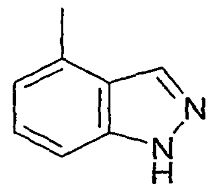
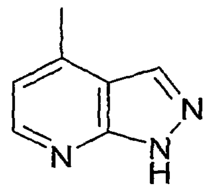
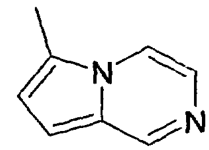
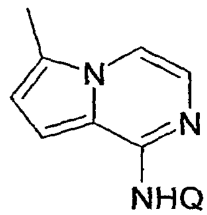
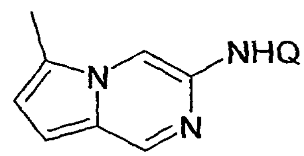
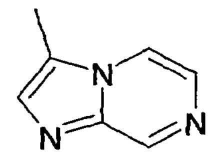
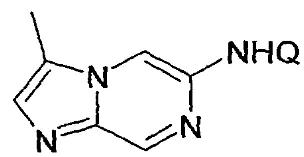
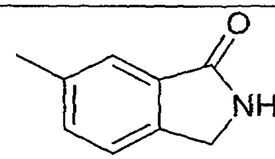
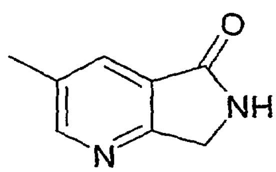
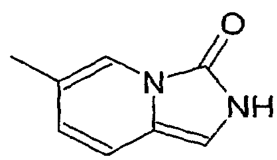
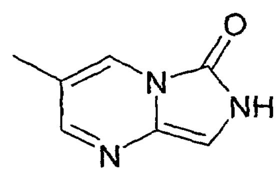
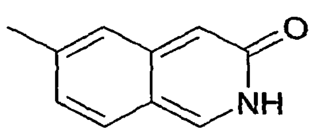
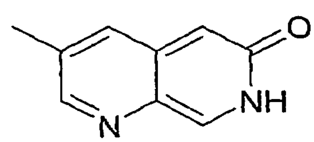
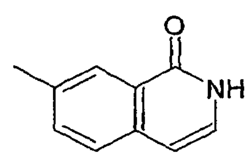
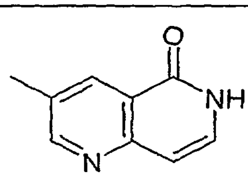
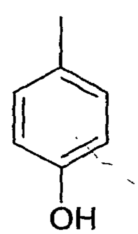
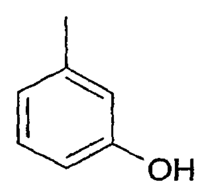
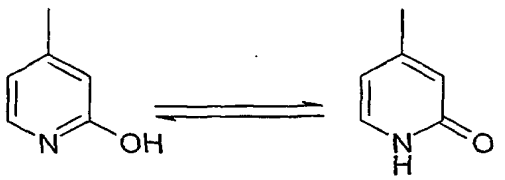
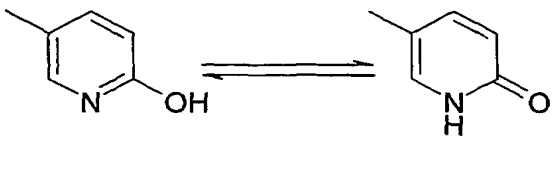
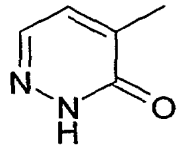
		
		
		
		
		
		

Table 1 -Examples of the Group R^1







In the formulae set out in Table 1, the moiety Q forming part of the amino group can be hydrogen, or can be selected from trifluoromethyl, carboxy, carbocyclic and heterocyclic groups having from 3 to 12 ring members; a group R^a-R^b wherein R^a is a bond, CO, $C(X^2)X^1$, SO_2; and R^b is selected from hydrogen, carbocyclic and heterocyclic groups having from 3 to 7 ring members, and a C_{1-8} hydrocarbyl group optionally substituted by one or more substituents selected from hydroxy, oxo, halogen, cyano, amino, mono- or di-C_{1-4} hydrocarbylamino, carbocyclic and heterocyclic groups having from 3 to 12 ring members and wherein one or more carbon atoms of the C_{1-8} hydrocarbyl group may optionally be replaced by O, S, SO, SO_2, NR^c, $X^1C(X^2)$, $C(X^2)X^1$ or $X^1C(X^2)X^1$;

R^c is selected from hydrogen and C_{1-4} hydrocarbyl; and

X^1 is O, S or NR^c and X^2 is =O, =S or =NR^c.

Where the substituent group Q comprises or includes a carbocyclic or heterocyclic group, the said carbocyclic or heterocyclic group may be unsubstituted or may itself be substituted with one or more further substituent groups R^{12} as hereinbefore defined. In one sub-group of compounds of the formula (I), such further substituent groups R^{11} may include carbocyclic or heterocyclic groups, which are typically not themselves further substituted. In another sub-group of compounds of the formula

(I), the said further substituents do not include carbocyclic or heterocyclic groups but are otherwise selected from the groups listed above in the definition of R^{12}.

The groups R^1 may be unsubstituted or substituted as shown in Table 1, or other substituents selected from the group R^{12} as hereinbefore defined may be present.

The groups R^2, R^3, R^4 and R^5 can each be selected from hydrogen and a group of substituents including a group R^{11}, and the groups A and E may each be optionally substituted by a group R^{11}, where R^{11} is saturated C_{1-6} hydrocarbyl optionally substituted by hydroxy or C_{1-4} hydrocarbyloxy. Preferred saturated hydrocarbyl groups are C_{1-4} alkyl groups, C_{3-4} cycloalkyl groups and C_{3-4} cycloalkylmethyl groups. Particular examples of such groups are methyl, ethyl, n-propyl, isopropyl, n-butyl, isobutyl, cyclopropyl, cyclopropylmethyl and cyclobutyl. The saturated hydrocarbyl groups may be substituted by hydroxy or C_{1-4} hydrocarbyloxy groups and examples of such substituents include methoxyethyl and ethoxyethyl.

In one general embodiment, R^2 is hydrogen.

In another general embodiment, R^4 is hydrogen.

The groups A and E are the same or different and each is an alkylene group of 2 or 3 carbon atoms in length optionally substituted by one or more groups selected from R^{11} and $-X-CH(R^6)(R^7)$. The groups A and E are attached to moieties R^3 and R^5 respectively

In general, it is preferred that no more than 3 substituent groups R^{11} are present on any one of A and E, and more preferably no more than 2 such groups are present. In one sub-group of compounds of the formula (I) or (II), no substituents R^{11} are present on A or E.

For example, when R^3 is hydrogen and no other substituents are present, the moiety $A-R^3$ can take the form $-CH_2-CH_2-$ or $-CH_2-CH_2-CH_2-$. Similarly, when R^5 is hydrogen and no other substituents are present, the moiety $E-R^5$ can take the form $-CH_2-CH_2-$ or $-CH_2-CH_2-CH_2-$.

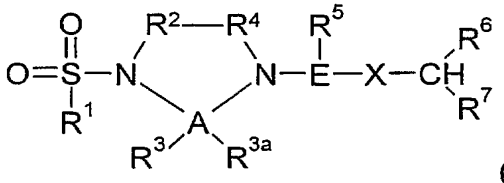
In an alternative embodiment of the invention, any one pair or any two non-overlapping pairs selected from R^2 and R^3; R^3 and R^4; R^2 and R^5; R^3 and R^5; R^4 and R^5; R^3 and R^8, and R^4 and R^8 are linked together in a ring and together form an alkylene chain of 1 to 5 carbon atoms in length which may be optionally substituted by one or more groups selected from R^{11} and $-X-CH(R^6)(R^7)$. In the present context, two pairs are regarded as overlapping where a member of one pair is interposed between the members of the other pair or where two pairs share a common group. For example, the two pairs R^2/R^3 and R^3/R^4 are overlapping whereas the two pairs R^2/R^3 and R^4/R^5 are non-overlapping. It is preferred that only one pair of groups selected from the above list are linked together to form a ring.

In a further embodiment, the pair of groups R^2 and R^4 may be are linked together in a ring and together form an alkylene chain of 2 to 5 carbon atoms in length which may be optionally substituted by one or more groups selected from R^{11} and $-X-CH(R^6)(R^7)$.

The alkylene chain formed by two linked groups selected from R^2, R^3, R^4; R^5 and R^8 may be from 1 to 5 carbon atoms in length, more usually from 1 to 3 carbon atoms in length. It will be appreciated that when two such groups are linked, a cyclic structure is formed that includes the nitrogen atom or alkylene group A/E to which the moieties R^2, R^3, R^4 and R^5 are attached. The cyclic structure preferably has 5 or 6 ring members.

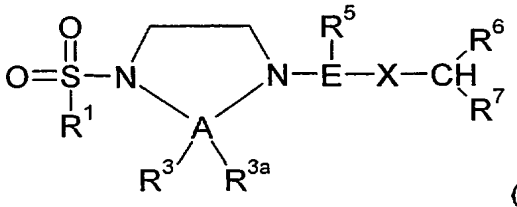
Particular sub-groups of compounds of the invention, in which the central diamine structure is varied, are represented by the formulae (III) to (VI) below, in which R^1 to R^7, E, A and X are as defined elsewhere in this specification.

In formula (III) below, R^2 and R^4 are linked to form a ring and together define an optionally substituted alkylene group of 2 or 3 carbon atoms (preferably 2) in length.



(III)

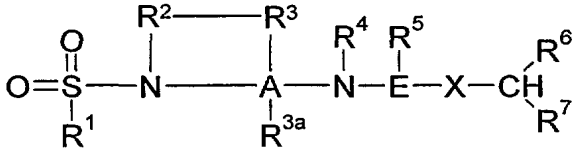
In one particular sub-group of compounds within the formula (III), the alkylene group is an unsubstituted alkylene chain, and examples of such compounds having an alkylene chain length of 2 can be represented by the formula (IIIa):



(IIIa)

In formula (IIIa), R^3 and R^5 are preferably hydrogen.

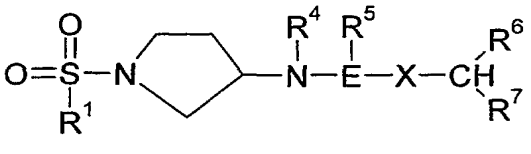
In formula (IV) below, R^2 and R^3 are linked to form a ring and together define an optionally substituted alkylene group having a chain length of 1, 2 or 3 (preferably 2) carbon atoms.



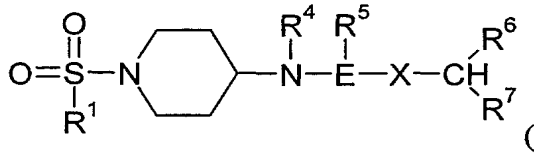
(IV)

In formula (IV), R^4 and R^5 preferably are hydrogen.

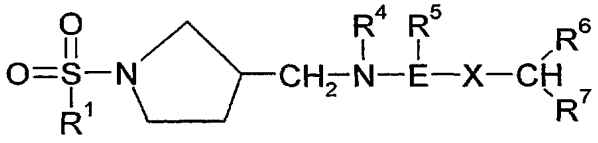
Examples of compounds of the formula (IV) wherein R^2 and R^3 together define an unsubstituted alkylene chain of 1 or 2 carbon atoms in length and A is an unsubstituted alkylene chain of 2 or 3 carbon atoms in length are represented by the formulae (IVa), (IVb), (IVc) and (IVd):



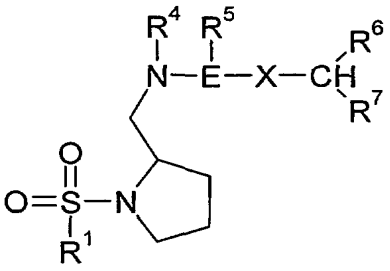
(IVa)



(IVb)

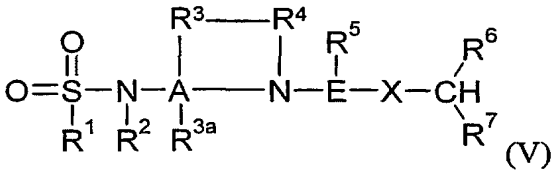


(IVc)



(IVd)

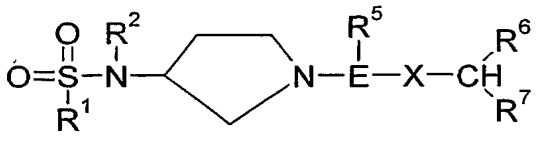
In formula (V) below, R^3 and R^4 are linked to form a ring and together define an alkylene group of 1, 2 or 3 carbon atoms (preferably 1 or 2) in length.



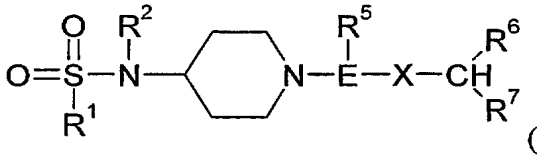
(V)

R^2 and R^5 preferably are hydrogen.

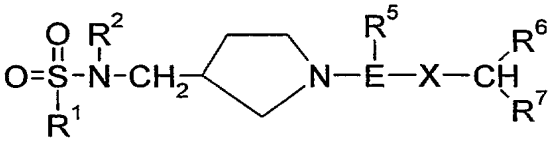
Examples of compounds of the formula (V) wherein R^3 and R^4 together form an unsubstituted alkylene chain and A is an alkylene chain of 2 or 3 carbon atoms in length are represented by the formulae (Va), (Vb), (Vc) and (Vd):



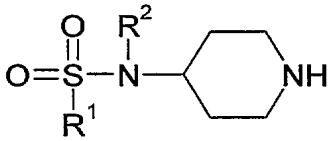
(Va)



(Vb)

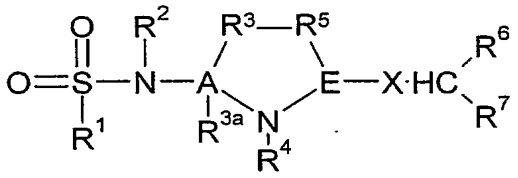


(Vc)



(Vd)

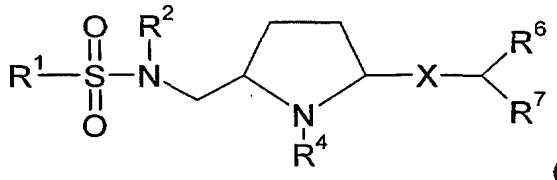
In formula (VI), R^3 and R^5 are linked to form a ring and together define an optionally substituted alkylene chain of 1, 2, 3 or 4 carbon atoms in length.



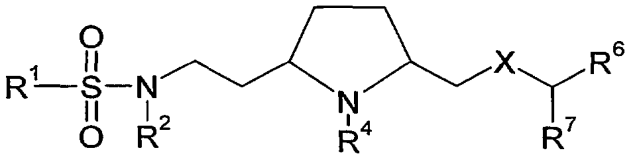
(VI)

In formula (VI), preferably the values for R^3, R^5, A and E are such that the resulting ring has from 5 to 7 ring members, more preferably 5 or 6.

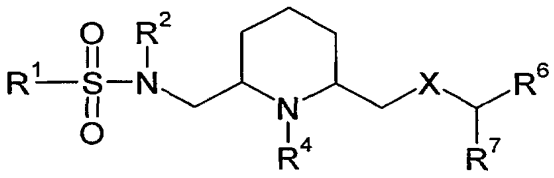
Examples of compounds of the formula (VI) wherein R^3 and R^5 together form an unsubstituted alkylene chain and A is an alkylene chain of 2 or 3 carbon atoms in length are represented by the formulae (VIa), (VIb), (VIc), (VId), (VIe) and (VIf).



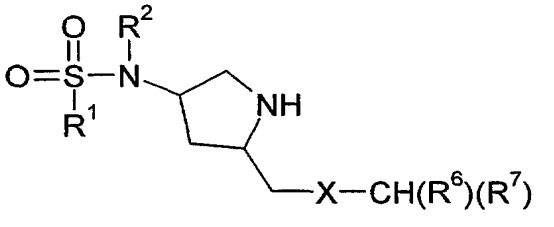
(VIa)



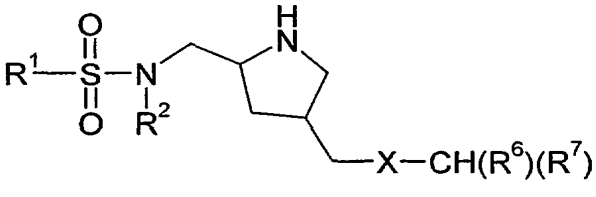
(VIb)



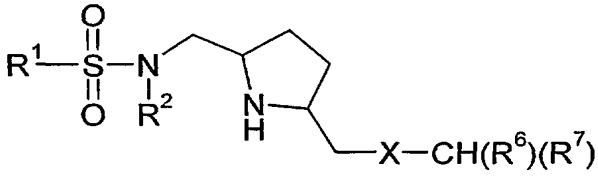
(VIc)



(VId)

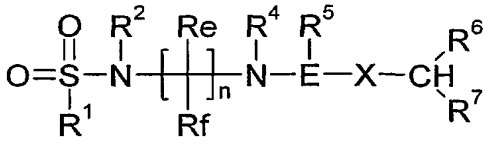


(VIe)



(VIf)

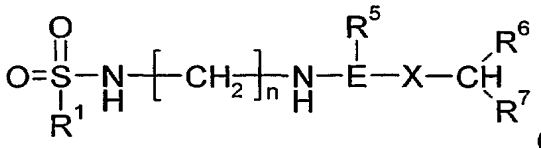
In formula (VII) below, R^e and R^f are the same or different and each is selected from hydrogen, R^{11} and $-X-CH(R^6)(R^7)$, and n is 2 or 3.



(VII)

In formula (VII), R^e and R^f are preferably hydrogen.

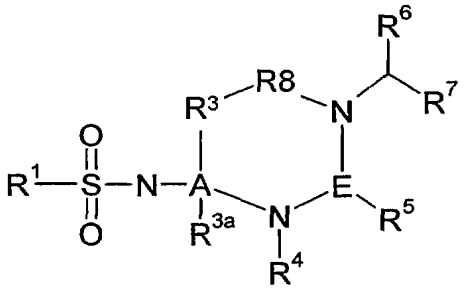
One particular sub-group of compounds within formula (VII) is represented by the formula (VIIa):



(VIIa)

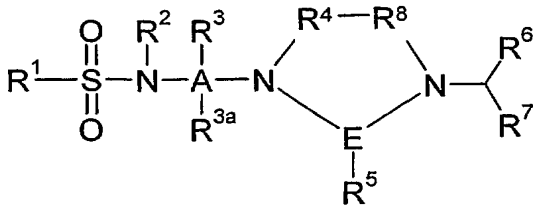
wherein n is 2 or 3.

In formula (VIII), R^3 and R^8 are linked to form a ring and together define an optionally substituted alkylene chain of 1, 2 or 3 carbon atoms in length.



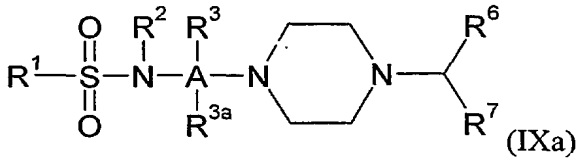
(VIII)

In formula (IX), R^4 and R^8 are linked to form a ring and together define an optionally substituted alkylene chain of 2 or 3 carbon atoms in length.



(IX)

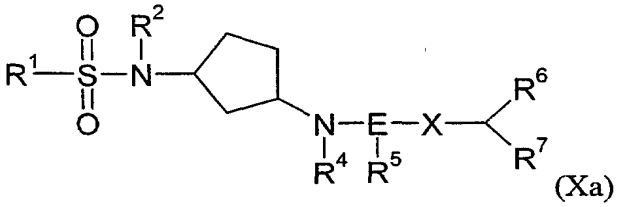
On particular group of compounds within formula (IX) is represented by the formula (IXa).



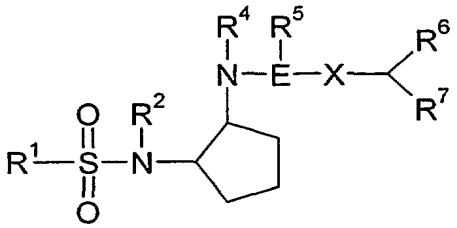
(IXa)

In one general embodiment, when R^4 and R^8 are linked to form a ring, R^1 may be other than an unsubstituted or substituted isoquinoline, particularly an isoquinolin-5-yl group.

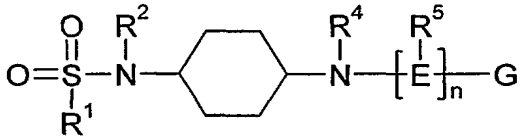
In formula (I) and each of the sub-groups thereof as hereinbefore defined, the substituent groups R^3 and R^{3a} can be linked together in a ring and may form an alkylene chain of 1 to 6 carbon atoms in length. The two groups R^3 and R^{3a} may be attached to the same carbon atom of the group A, thereby forming a spiro-ring, but more preferably they are attached to different carbon atoms of the group A. Examples of compounds in which R^3 and R^{3a} are linked together in a ring are represented by formula (Xa), (Xb) and (Xc).



(Xa)

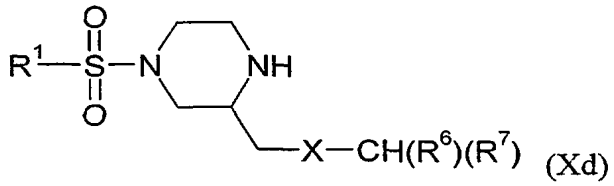


(Xb)



(Xc)

An example of a group of compounds wherein R^2 and R^5 are linked together in a ring is shown in Formula (Xd):



(Xd)

The heteroatomic moiety X in Formula (I) and its sub-groups is selected from O, S, SO, SO_2 and NR^8. Preferably X is O or NR^8 wherein R^8 is hydrogen, and more preferably X is O.

The groups R^6 and R^7 are the same or different and each is selected from hydrogen, saturated C_{1-6} hydrocarbyl, trifluoromethyl, cyano; $CONR^9R^{10}$ and aryl and heteroaryl groups having from 5 to 12 ring members; or R^6 and R^7 together with the carbon atom to which they are attached form a carbocyclic or heterocyclic group having from 5 to 12 ring members.

When R^6 and/or R^7 are aryl and heteroaryl groups, they can be selected from any of the aryl and heteroaryl groups listed above in relation to the group R^1. Unless the context indicates otherwise, the preferences and specific examples given for the group R^1 apply also to the groups R^6 and R^7. The aryl and heteroaryl groups may be unsubstituted or substituted by one or more substituent groups R^{12} as hereinbefore defined.

One or both of R^6 and R^7 may be aryl or heteroaryl groups. In one particular embodiment, only one of the groups R^6 and R^7 is aryl or heteroaryl and the other is hydrogen or an optionally substituted C_{1-6} hydrocarbyl group.

In one particular combination of substituents, R^6 is an optionally substituted phenyl group and R^7 is hydrogen.

The phenyl group can be substituted with, for example, a substituent group selected from halogen, C_{1-8} hydrocarbyl, C_{1-8} hydrocarbyloxy, hydroxy, trifluoromethyl,

cyano, nitro and amino, currently preferred substituent groups including halogen and alkyl.

For the avoidance of doubt, it is to be understood that the general and specific preferences, embodiments and examples set out above for any one of the groups R^1, R^2, R^3, R^{3a}, R^4, R^5, R^6, R^7, E, A and X may be combined with each general and specific preference, embodiment and example of any one or more of the other said groups and that all such combinations are embraced by this application.

Particular novel compounds of the invention are:
isoquinoline-5-sulphonic acid [2-(2-benzyloxy-ethylamino)-ethyl]-amide;
isoquinoline-5-sulphonic acid {2-[2-(4-chloro-benzyloxy)-ethylamino]-ethyl}-amide;
isoquinoline-5-sulphonic acid {2-[2-(2-chloro-benzyloxy)-ethylamino]-ethyl}-amide;
isoquinoline-5-sulphonic acid {2-[2-(3-chloro-benzyloxy)-ethylamino]-ethyl}-amide;
isoquinoline-5-sulphonic acid {2-[2-(2-methyl-benzyloxy)-ethylamino]-ethyl}-amide;
isoquinoline-5-sulphonic acid {2-[2-(3-methyl-benzyloxy)-ethylamino]-ethyl}-amide;
isoquinoline-5-sulphonic acid {2-[2-(4-methyl-benzyloxy)-ethylamino]-ethyl}-amide;
N-[2-(2-Benzyloxy-ethylamino)-ethyl]-3-nitro-benzenesulphonamide;
isoquinoline-5-sulphonic acid (pyrrolidin-3-yl)-amide;
isoquinoline-5-sulphonic acid (pyrrolidin-2-ylmethyl)-amide;
isoquinoline-5-sulphonic acid {2-[2-(2-methoxy-benzyloxy)-ethylamino]-ethyl}-amide;
isoquinoline-5-sulphonic acid {2-[2-(3-methoxy-benzyloxy)-ethylamino]-ethyl}-amide;
isoquinoline-5-sulphonic acid {2-[2-(4-methoxy-benzyloxy)-ethylamino]-ethyl}-amide;

isoquinoline-5-sulphonic acid {2-[2-(3,4-dichloro-benzyloxy)-ethylamino]-ethyl}-amide;
isoquinoline-5-sulphonic acid {2-[2-(3-nitro-benzyloxy)-ethylamino]-ethyl}-amide;
isoquinoline-5-sulphonic acid {2-[2-(3-acetamido-benzyloxy)-ethylamino]-ethyl}-amide;
isoquinoline-5-sulphonic acid piperidin-4-ylamide;
1-(isoquinoline-5-sulphonyl)-piperidin-4-ylamine;
2-(3,4-dichloro-benzyloxy)-ethyl]-[1-(isoquinoline-5-sulphonyl)-piperidin-4-yl]-amine;
isoquinoline-5-sulphonic acid piperidin-3-ylamide;
5-[3-(4-chloro-benzyloxymethyl)-piperazine-1-sulphonyl]-isoquinoline;
isoquinoline-5-sulphonic acid [5-(S)-(4-chlorobenzyloxymethyl)pyrrolidin-3-(R)-yl]methoxymethyl amide;
isoquinoline-5-sulphonic acid [5-(S)-(4-chlorobenzyloxymethyl)pyrrolidin-3-(R)-yl] amide;
isoquinoline-5-sulphonic acid [5-(S)-(4-chlorobenzyloxymethyl)pyrrolidin-3-(R)-yl] amide;
isoquinoline-5-sulphonic acid [4-(R)-(4-chlorobenzyloxy)pyrrolidin-2-(S)-ylmethyl]amide;
isoquinoline-5-sulphonic acid [4-(S)-(benzyloxy)pyrrolidin-2-(S)-ylmethyl]amide;
isoquinoline-5-sulphonic acid [4-(S)-(4-chlorobenzyloxy)pyrrolidin-2-(S)-ylmethyl]amide;
isoquinoline-5-sulphonic acid [*cis*-5-(4-chlorobenzyloxymethyl)pyrrolidin-2-ylmethyl]amide; and
isoquinoline-5-sulphonic acid (*trans*-4-amino-cyclohexyl)-amide.

Unless otherwise specified, a reference to a particular compound also includes ionic, salt, solvate, and protected forms thereof, for example, as discussed below.

Many compounds of the formulae (I^0) and (I) can exist in the form of salts, for example acid addition salts or, in certain cases salts of organic and inorganic bases such as carboxylate, sulphonate and phosphate salts. All such salts are within the

scope of this invention, and references to compounds of the formulae (I^0) and (I) include the salt forms of the compounds. In this and the following sections of this application, all references to formula (I) should be taken to refer also to formula (I^0) and sub-formulae thereof unless the context indicates otherwise.

Salt forms may be selected and prepared according to methods described in *Pharmaceutical Salts: Properties, Selection, and Use*, P. Heinrich Stahl (Editor), Camille G. Wermuth (Editor), ISBN: 3-90639-026-8, Hardcover, 388 pages, August 2002.

Acid addition salts may be formed with a wide variety of acids, both inorganic and organic. Examples of acid addition salts include salts formed with acetic, 2,2-dichloroacetic, adipic, alginic, ascorbic (e.g. L-ascorbic), L-aspartic, benzenesulphonic, benzoic, 4-acetamidobenzoic, butanoic, (+) camphoric, camphor-sulphonic, (+)-(1*S*)-camphor-10-sulphonic, capric, caproic, caprylic, cinnamic, citric, cyclamic, dodecylsulphuric, ethane-1,2-disulphonic, ethanesulphonic, 2-hydroxyethanesulphonic, formic, fumaric, galactaric, gentisic, glucoheptonic, D-gluconic, glucuronic (e.g. D-glucuronic), glutamic (e.g. L-glutamic), α-oxoglutaric, glycolic, hippuric, hydrobromic, hydrochloric, hydriodic, isethionic, (+)-L-lactic, (±)-DL-lactic, lactobionic, maleic, malic, (-)-L-malic, malonic, (±)-DL-mandelic, methanesulphonic, naphthalene-2-sulphonic, naphthalene-1,5-disulphonic, 1-hydroxy-2-naphthoic, nicotinic, nitric, oleic, orotic, oxalic, palmitic, pamoic, phosphoric, propionic, L-pyroglutamic, salicylic, 4-amino-salicylic, sebacic, stearic, succinic, sulphuric, tannic, (+)-L-tartaric, thiocyanic, *p*-toluenesulphonic, undecylenic and valeric acids, as well as acylated amino acids and cation exchange resins.

One particular group of salts consists of salts formed from hydrochloric, hydriodic, phosphoric, nitric, sulphuric, citric, lactic, succinic, maleic, malic, isethionic, fumaric, benzenesulphonic, toluenesulphonic, methanesulphonic, ethanesulphonic, naphthalenesulphonic, valeric, acetic, propanoic, butanoic, malonic, glucuronic and lactobionic acids.

When the compound is anionic, or has a functional group which may be anionic (e.g., -COOH may be -COO^-), then a salt may be formed with a suitable cation. Examples of suitable inorganic cations include, but are not limited to, alkali metal ions such as Na^+ and K^+, alkaline earth cations such as Ca^{2+} and Mg^{2+}, and other cations such as Al^{3+}. Examples of suitable organic cations include, but are not limited to, ammonium ion (i.e., NH_4^+) and substituted ammonium ions (e.g., NH_3R^+, $NH_2R_2^+$, NHR_3^+, NR_4^+). Examples of some suitable substituted ammonium ions are those derived from: ethylamine, diethylamine, dicyclohexylamine, triethylamine, butylamine, ethylenediamine, ethanolamine, diethanolamine, piperazine, benzylamine, phenylbenzylamine, choline, meglumine, and tromethamine, as well as amino acids, such as lysine and arginine. An example of a common quaternary ammonium ion is $N(CH_3)_4^+$.

Where the compounds of the formula (I) contain an amine function, these may form quaternary ammonium salts, for example by reaction with an alkylating agent according to methods well known to the skilled person. Such quaternary ammonium compounds are within the scope of formula (I).

The salt forms of the compounds of the invention are typically pharmaceutically acceptable salts, and examples of pharmaceutically acceptable salts are discussed in Berge *et al.*, 1977, "Pharmaceutically Acceptable Salts," *J. Pharm. Sci.*, Vol. 66, pp. 1-19. However, salts that are not pharmaceutically acceptable may also be prepared as intermediate forms which may then be converted into pharmaceutically acceptable salts. Such non-pharmaceutically acceptable salts forms, which may be useful, for example, in the purification or separation of the compounds of the invention, also form part of the invention

Compounds of the formula (I) containing an amine function may also form N-oxides. A reference herein to a compound of the formula (I) that contains an amine function also includes the N-oxide.

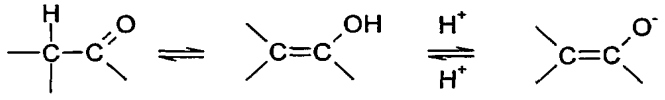
Where a compound contains several amine functions, one or more than one nitrogen atom may be oxidised to form an N-oxide. Particular examples of N-

oxides are the N-oxides of a tertiary amine or a nitrogen atom of a nitrogen-containing heterocycle.

N-Oxides can be formed by treatment of the corresponding amine with an oxidizing agent such as hydrogen peroxide or a per-acid (e.g. a peroxycarboxylic acid), see for example *Advanced Organic Chemistry*, by Jerry March, 4th Edition, Wiley Interscience, pages. More particularly, N-oxides can be made by the procedure of L. W. Deady (*Syn. Comm.* 1977, 7, 509-514) in which the amine compound is reacted with *m*-chloroperoxybenzoic acid (MCPBA), for example, in an inert solvent such as dichloromethane.

Compounds of the formula may exist in a number of different geometric isomeric, and tautomeric forms and references to compounds of the formula (I) include all such forms. For the avoidance of doubt, where a compound can exist in one of several geometric isomeric or tautomeric forms and only one is specifically described or shown, all others are nevertheless embraced by formula (I).

Other examples of tautomeric forms include, for example, keto-, enol-, and enolate-forms, as in, for example, the following tautomeric pairs: keto/enol (illustrated below), imine/enamine, amide/imino alcohol, amidine/amidine, nitroso/oxime, thioketone/enethiol, and nitro/aci-nitro.



keto enol enolate

Where compounds of the formula (I) contain one or more chiral centres, and can exist in the form of two or more optical isomers, references to compounds of the formula (I) include all optical isomeric forms thereof (e.g. enantiomers, epimers and diastereoisomers), either as individual optical isomers, or mixtures (e.g. racemic mixtures) or two or more optical isomers, unless the context requires otherwise.

The optical isomers may be characterised and identified by their optical activity (i.e. as + and – isomers, or *d* and *l* isomers) or they may be characterised in terms of

their absolute stereochemistry using the "R and S" nomenclature developed by Cahn, Ingold and Prelog, see *Advanced Organic Chemistry* by Jerry March, 4th Edition, John Wiley & Sons, New York, 1992, pages 109-114, and see also Cahn, Ingold & Prelog, *Angew. Chem. Int. Ed. Engl.*, 1966, 5, 385-415.

Optical isomers can be separated by a number of techniques including chiral chromatography (chromatography on a chiral support) and such techniques are well known to the person skilled in the art.

Where compounds of the formula (I) exist as two or more optical isomeric forms, one enantiomer in a pair of enantiomers may exhibit advantages over the other enantiomer, for example, in terms of biological activity. Thus, in certain circumstances, it may be desirable to use as a therapeutic agent only one of a pair of enantiomers, or only one of a plurality of diastereoisomers. Accordingly, the invention provides compositions containing a compound of the formula (I) having one or more chiral centres, wherein at least 55% (e.g. at least 60%, 65%, 70%, 75%, 80%, 85%, 90% or 95%) of the compound of the formula (I) is present as a single optical isomer (e.g. enantiomer or diastereoisomer). In one general embodiment, 99% or more (e.g. substantially all) of the total amount of the compound of the formula (I) may be present as a single optical isomer (e.g. enantiomer or diastereoisomer).

The compounds of the invention include compounds with one or more isotopic substitutions, and a reference to a particular element includes within its scope all isotopes of the element. For example, a reference to hydrogen includes within its scope ^{1}H, ^{2}H (D), and ^{3}H (T). Similarly, references to carbon and oxygen include within their scope respectively ^{12}C, ^{13}C and ^{14}C and ^{16}O and ^{18}O.

The isotopes may be radioactive or non-radioactive. In one embodiment of the invention, the compounds contain no radioactive isotopes. Such compounds are preferred for therapeutic use. In another embodiment, however, the compound may contain one or more radioisotopes. Compounds containing such radioisotopes may be useful in a diagnostic context.

Esters such as carboxylic acid esters and acyloxy esters of the compounds of formula (I) bearing a carboxylic acid group or a hydroxyl group are also embraced by Formula (I). Examples of esters are compounds containing the group -C(=O)OR, wherein R is an ester substituent, for example, a C_{1-7} alkyl group, a C_{3-20} heterocyclyl group, or a C_{5-20} aryl group, preferably a C_{1-7} alkyl group. Particular examples of ester groups include, but are not limited to, $-C(=O)OCH_3$, $-C(=O)OCH_2CH_3$, $-C(=O)OC(CH_3)_3$, and -C(=O)OPh. Examples of acyloxy (reverse ester) groups are represented by -OC(=O)R, wherein R is an acyloxy substituent, for example, a C_{1-7} alkyl group, a C_{3-20} heterocyclyl group, or a C_{5-20} aryl group, preferably a C_{1-7} alkyl group. Particular examples of acyloxy groups include, but are not limited to, $-OC(=O)CH_3$ (acetoxy), $-OC(=O)CH_2CH_3$, $-OC(=O)C(CH_3)_3$, -OC(=O)Ph, and $-OC(=O)CH_2Ph$.

Also encompassed by formula (I) are any polymorphic forms of the compounds, solvates (e.g. hydrates), complexes (e.g. inclusion complexes or clathrates with compounds such as cyclodextrins, or complexes with metals) of the compounds, and pro-drugs of the compounds. By "prodrugs" is meant for example any compound that is converted *in vivo* into a biologically active compound of the formula (I).

For example, some prodrugs are esters of the active compound (e.g., a physiologically acceptable metabolically labile ester). During metabolism, the ester group (-C(=O)OR) is cleaved to yield the active drug. Such esters may be formed by esterification, for example, of any of the carboxylic acid groups (-C(=O)OH) in the parent compound, with, where appropriate, prior protection of any other reactive groups present in the parent compound, followed by deprotection if required.

Examples of such metabolically labile esters include those of the formula -C(=O)OR wherein R is:

C_{1-7}alkyl

(e.g., -Me, -Et, -nPr, -iPr, -nBu, -sBu, -iBu, -tBu);

C_{1-7}aminoalkyl

(e.g., aminoethyl; 2-(N,N-diethylamino)ethyl; 2-(4-morpholino)ethyl); and

acyloxy-C_{1-7}alkyl
(e.g., acyloxymethyl;
acyloxyethyl;
pivaloyloxymethyl;
acetoxymethyl;
1-acetoxyethyl;
1-(1-methoxy-1-methyl)ethyl-carbonxyloxyethyl;
1-(benzoyloxy)ethyl; isopropoxy-carbonyloxymethyl;
1-isopropoxy-carbonyloxyethyl; cyclohexyl-carbonyloxymethyl;
1-cyclohexyl-carbonyloxyethyl;
cyclohexyloxy-carbonyloxymethyl;
1-cyclohexyloxy-carbonyloxyethyl;
(4-tetrahydropyranyloxy) carbonyloxymethyl;
1-(4-tetrahydropyranyloxy)carbonyloxyethyl;
(4-tetrahydropyranyl)carbonyloxymethyl; and
1-(4-tetrahydropyranyl)carbonyloxyethyl).

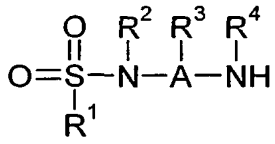
Also, some prodrugs are activated enzymatically to yield the active compound, or a compound which, upon further chemical reaction, yields the active compound (for example, as in ADEPT, GDEPT, LIDEPT, etc.). For example, the prodrug may be a sugar derivative or other glycoside conjugate, or may be an amino acid ester derivative.

Methods for the Preparation of Compounds of the Formula (I)

Compounds of the formula (I) can be prepared by various synthetic routes as set out below.

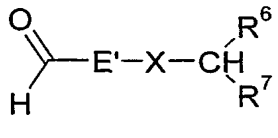
General Synthetic Route 1

Compounds of the formula (I) can be prepared by the reaction of a compound of the formula (XI):



(XI)

with an aldehyde of the formula(XII):

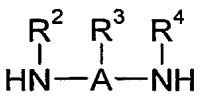


(XII)

wherein E' is an alkylene group of 1 or 2 carbon atoms in length (e.g. a group $(CH_2)_r$ where r is 1 or 2) optionally substituted by one or more groups selected from R^{11} and $-X-CH(R^6)(R^7)$ where X, R^1 to R^4, R^6, R^7 and R^{11} are as hereinbefore defined, under reductive amination conditions.

The reductive amination is carried out by mixing the amine (XI) and the aldehyde (XII) in a suitable solvent, for example an alcohol such as methanol or a chlorinated solvent (or mixture of solvents) such as dichloromethane and 1,2-dichoromethane, at a non-extreme temperature, for example room temperature. Reduction of the intermediate adduct formed between the amine and aldehyde is effected using a reducing agent such as a borohydride derivative. Examples of borohydride derivatives that can be used include sodium cyanoborohydride and sodium triacetoxyborohydride, optionally in the presence of a catalytic amount of acetic acid.

Amines of the formula (XI) can be prepared by coupling together aromatic or heteroaromatic sulphonyl chlorides of the formula R^1SO_2Cl with an amine of the formula (XIII):

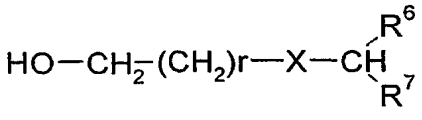


(XIII)

wherein R^2, R^3 and R^4 are as hereinbefore defined.

The coupling reaction is typically carried out in a non-protic solvent such as dichloromethane using an excess of the amine. Alternatively, instead of using an excess of the amine, a molar equivalent of the amine may be used together with a non-reacting amine such as triethylamine. Many aromatic and heteroaromatic sulphonyl chlorides are available commercially but, where they are not commercially available, they can be prepared by treating the corresponding sulphonic acids with thionyl chloride or oxalyl chloride under standard conditions or conditions analogous thereto. The sulphonic acids may in turn be obtained commercially or prepared by sulphonation of the aromatic or heteroaromatic nucleus according to methods well known in the art of organic chemistry.

The aldehydes of the formula (XII) can be prepared in a two step process starting from a halide of the formula R^6R^7HC-Hal, where "Hal" is a halogen such as bromine. In the first step, the halide is reacted with a compound (such as a glycol) of the formula $HO\text{-}CH_2\text{-}(CH_2)_r\text{-}XH$ in a nucleophilic displacement reaction to give an alcohol of the formula (XIV):



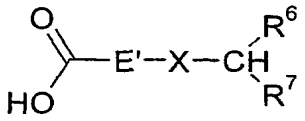
(XIV)

The reaction is typically carried out in a polar aprotic solvent such as tetrahydrofuran (THF) in the presence of a base such as sodium hydride. Typical conditions for reactions of a halide with a glycol are described in White, *J. Amer. Chem. Soc.*, 2002, 124, 4950-4951.

The alcohol (XIV) can be converted to the aldehyde (XII) by oxidation with a suitable oxidizing agent. For example, the oxidation may be carried using the Dess Martin periodinate or tetrapropylammonium perruthenate (TPAP) [*J. Org. Chem.*, 1983, 48, 4155-4156, and *Chem. Commun.* 1987, 1625].

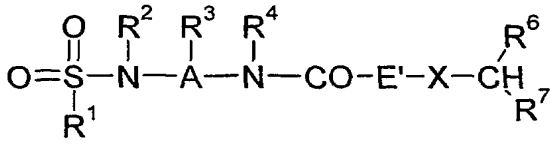
General Synthetic Route 2

In an alternative method of preparing compounds of the formula (I), an amine of the formula (XI) is first coupled with a compound of the formula (XV):



(XV)

using a suitable amide coupling reagent to give an amide of the formula (XVI):



(XVI)

where X, E', R^1 to R^4, R^6 and R^7 are as hereinbefore defined.

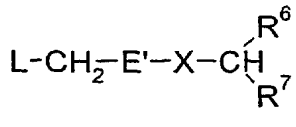
The amide coupling reaction can be carried out using isobutyl chloroformate or can be carried out in the presence of an amide coupling reagent of the type commonly used to form peptide linkages. Examples of such reagents include 1,3-dicyclohexylcarbodiimide (DCC) (Sheehan *et al, J. Amer. Chem Soc.* 1955, 77, 1067), 1-ethyl-3-(3'-dimethylaminopropyl)carbodiimide (EDC) (Sheehan *et al, J. Org. Chem., 1961, 26, 2525*), uronium-based coupling agents such as *O*-(7-azabenzotriazol-1-yl)-*N,N,N',N'*-tetramethyluronium hexafluorophosphate (HATU) (L. A. Carpino, *J. Amer. Chem. Soc.*, 1993, 115, 4397) and phosphonium-based coupling agents such as 1-benzo-triazolyloxytris(pyrrolidino)phosphonium hexafluorophosphate (PyBOP) (Castro *et al, Tetrahedron Letters*, 1990, 31, 205).

Alternatively, the amine (XI) can be reacted with the corresponding acid chloride under standard conditions. The acid chloride can be prepared from the acid by known methods, for example by treatment with oxalyl chloride and dimethylformamide or by reaction of a salt of the acid with oxalyl chloride.

The amide (XVI) can then be reduced to give the compound of formula (I) using a suitable reducing agent such as lithium aluminium hydride in a polar non-protic solvent such as tetrahydrofuran (THF).

General Synthetic Route 3

In a further alternative, compounds of the formula (I) can be prepared by reacting an amine of the formula (XI) with a compound of the formula (XVII):



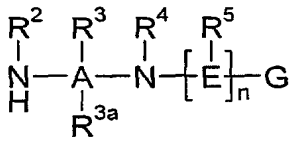
(XVII)

where E', X, R^6 and R^7 are as hereinbefore defined, and L is a leaving group such as bromine.

Compounds of the formula (XVII) wherein L is bromine may be prepared by reaction of an alcohol of the formula (XIV) with a bromine transfer reagent under conditions well known to the skilled chemist.

General Synthetic Route 4

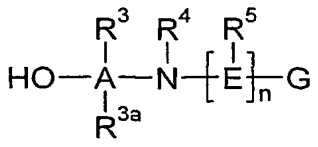
In another method of preparing compounds of the formula (I), an aromatic or heteroaromatic sulphonyl chloride of the formula R^1SO_2Cl is reacted with an amine of the formula (XVIII):



(XVIII)

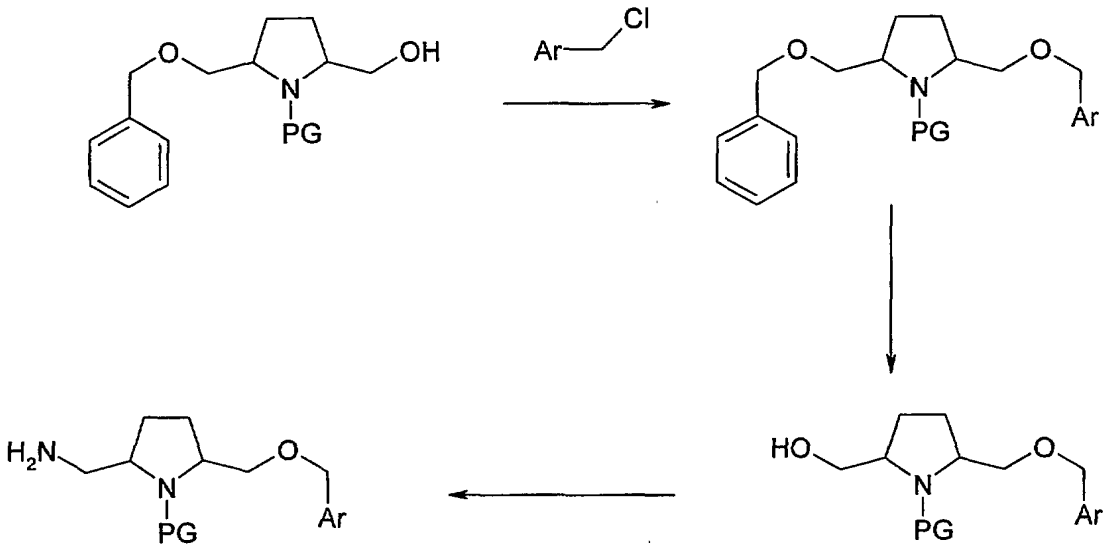
The reaction can be carried out using the conditions and reagents described above for the preparation of the compound (XI).

Amines of the formula (XVIII) can be prepared from commonly available starting materials using synthetic methods well known to the skilled person. For example, compounds wherein R^2 is hydrogen may be prepared from the corresponding compound of the formula (XIX):



(XIX)

or an appropriately protected form thereof, using standard literature methods for the conversion of alcohols to amines. Examples of such methods include replacement or derivatisation of the hydroxyl group to introduce leaving groups such as bromine or a mesylate which can be displaced with azide or phthalimide and then converted to the amine by reduction or treatment with hydrazine respectively. Illustrative of this approach is the route set out in Scheme 1 which shows the preparation of compounds of the formula (I) in which R^2, R^{3a} and R^4 are each hydrogen, and R^3 and R^5 are linked to form a pyrrolidine ring.

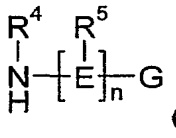


Scheme 1

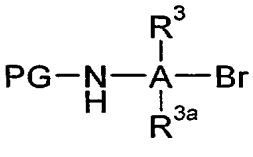
In Scheme 1, a pyrrolidine having hydroxymethyl and benzyloxymethyl substituents in the 2- and 5- positions and a protecting group on the nitrogen atom is used as the starting material. Compounds of this type can be made using the methods described in Q. Wang *et al.*, *J. Org. Chem.*, 1999, 64, 8602-8607. The protected hydroxymethyl pyrrolidine compound is then reacted in the presence of a base such as sodium hydride with an aryl- or heteroarylmethyl chloride suitable for

introducing a group R^6 or R^7 to give an arylmethoxy compound. The benzyl-protected hydroxyl group of the arylmethoxy compound is then removed by standard methods and the resulting alcohol is converted to an amino group by the methods described above. The pyrrolidine amine, in which the pyrrolidine nitrogen is protected, is then reacted with the sulphonyl chloride R^1SO_2Cl using the conditions described above to give a protected form of the compound of the formula (I) which may subsequently be deprotected by standard methods.

Amine compounds of the formula (XVIII) can also be prepared from compounds of the formula (XX) by reaction with a compound of the formula (XXI), in which PG is a protecting group.

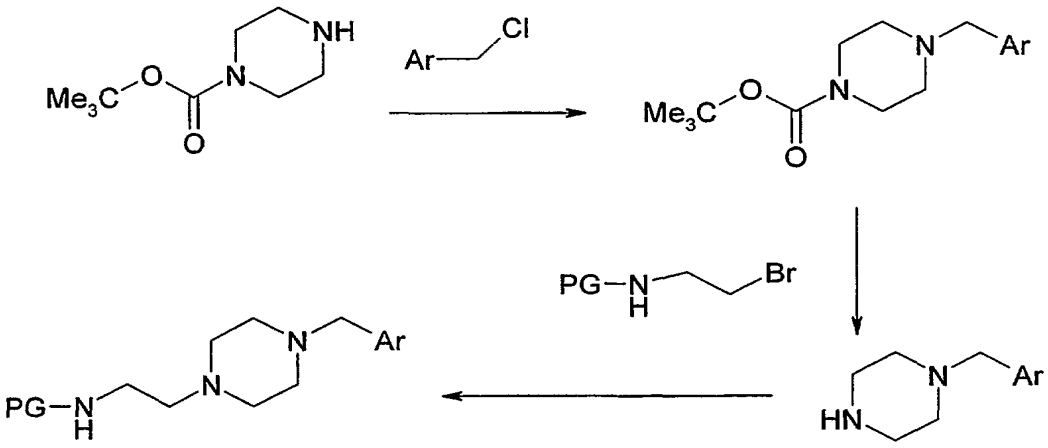


(XX)



(XXI)

Illustrative of this approach is the route set out in Scheme 2 which shows the preparation of compounds of the formula (I) in which R^2, R^3, R^{3a} and R^5 are each hydrogen, and R^4 and R^8 are linked to form a piperazine ring.



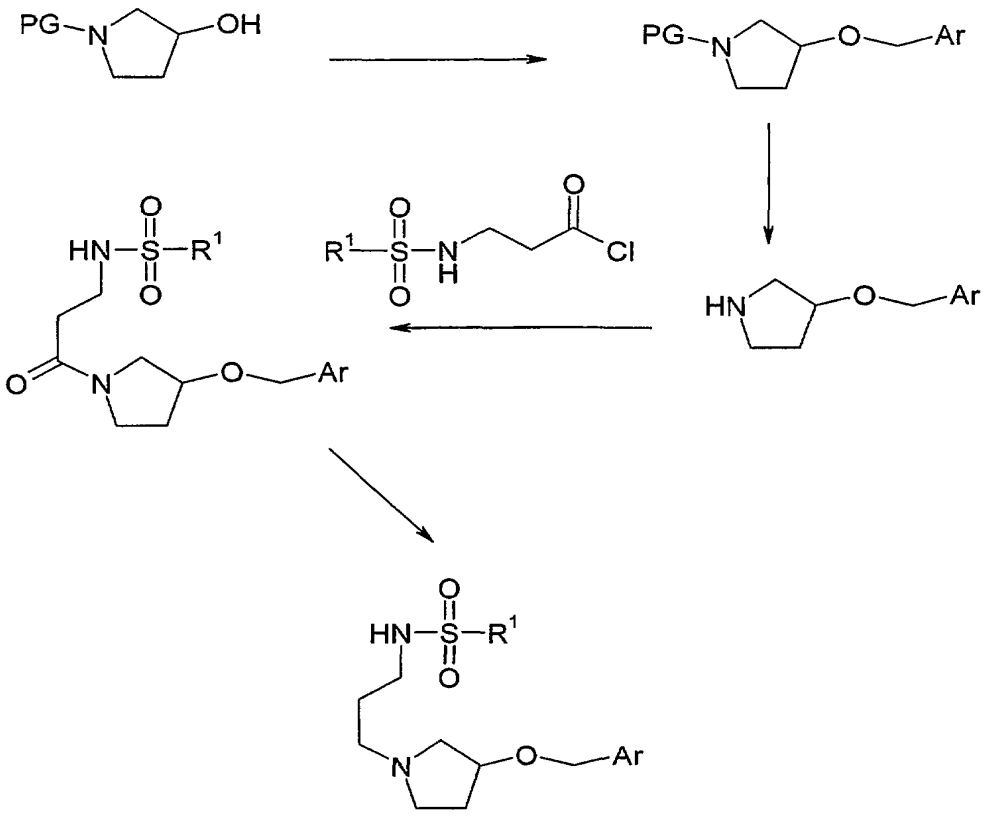
Scheme 2

In Scheme 2, a piperazine in which one nitrogen is protected by means of a suitable protecting group (in this case a tertiary-butyloxycarbonyl (Boc) group) is reacted with an aryl- or heteroarylmethyl chloride suitable for introducing a group R^6 or R^7 in the presence of a base to give an arylmethyl (or heteroarylmethyl) derivative of piperazine. The arylmethyl or heteroarylmethyl derivative is then deprotected by removal of the Boc group and the unprotected nitrogen is reacted with an N-protected 2-bromoethylamine PG-NH-$(CH_2)_2$-Br, in which PG is a protecting group, to give a protected amine of the formula (XVIII). Removal of the protecting group PG and reaction of the deprotected amine with the sulphonyl chloride R^1SO_2Cl using the conditions described above gives a compound of the formula (I).

The reaction sequences shown in Schemes 1 and 2 are merely exemplary and it will readily be apparent that changing the starting materials will give access to a variety of different amines of the formula (XVIII). For example, by replacing the piperazine starting material of Scheme 2 with a suitably protected 3-pyrrolidinol, amines can be prepared that can be reacted with the sulphonyl chloride R^1SO_2Cl to give a compound of the formula (I) in which X is O and R^4 and R^5 are linked together to form a pyrrolidine ring.

General Synthetic Route 5

A modified version of Synthetic Route 4, in which the group A is created by reduction of an amide bond, is shown in Scheme 3.

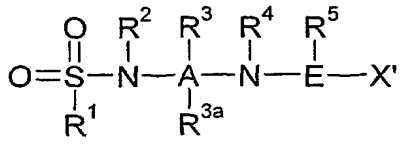


Scheme 3

In Scheme 3, an N-protected 3-hydroxypyrrolidine is reacted with an aryl- or heteroaryl halide in the presence of a base to give an arylmethoxy- or heteoarylmethoxy pyrrolidine which is then reacted with a heteroarylsulphonamido-propanoic acid (e.g. under the amide coupling conditions given above) or a reactive derivative thereof such as the acid chloride shown in Scheme 3. The resulting heteroarylsulphonamido-propanoyl pyrrolidine can then be reduced (e.g. using lithium aluminium hydride) to give the heteroarylsulphonamido-propyl pyrrolidine compound of the formula (I).

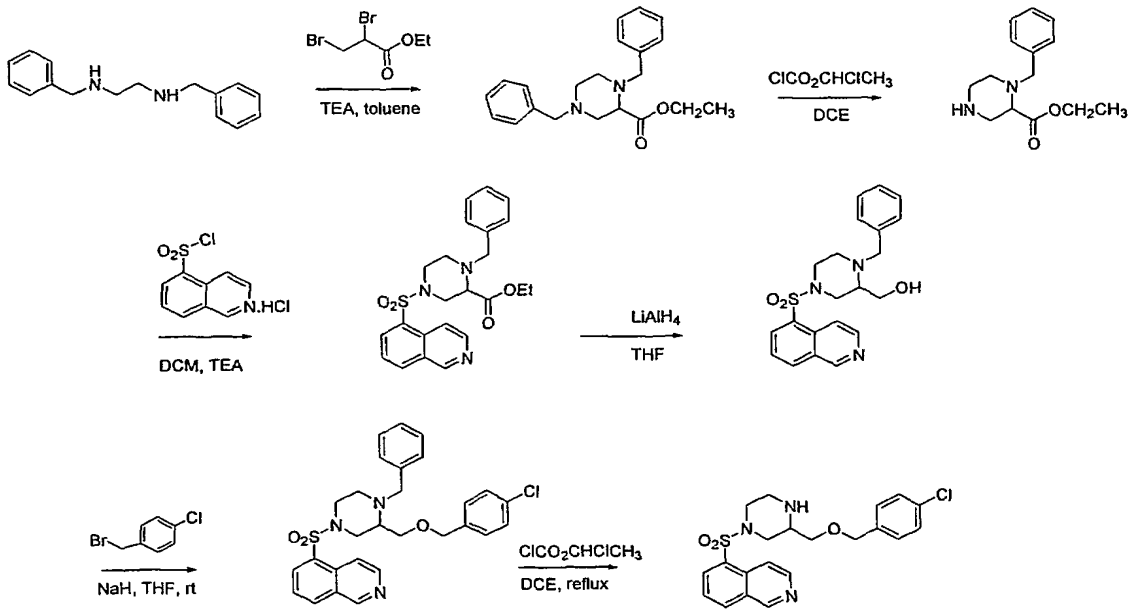
General Synthetic Route 6

Another synthetic route to compounds of the formula (I) involves the reaction of a compound of the formula (XXII):



(XXII)

or a protected form thereof, wherein R^1 to R^2, A and E are as hereinbefore defined, and X' is OH, NH_2 or SH, with a compound of the formula L-CH (R^6)(R^7) where L is a leaving group such as bromine, and thereafter removing any protecting group present. Illustrative of this approach is the route set out in Scheme 5 below.



Scheme 5

In Scheme 5, N'dibenzyl-1,2-diaminoethane is reacted with a 2,3-dibromo-propionic acid ester to give an N-protected piperazine ring bearing an ethoxycarbonyl substituent group. One of the benzyl protecting groups is then selectively removed by reaction with 1-chloroethyl chloroformate (see Bingwei V. Yang *et al. Synlett*, 1993; 195-196) in a halogenated solvent such as 1,2-dichloroethane (DCE). The partially deprotected piperazine can then be converted to a sulphonamide by reaction with isoquinolinylsulphonyl chloride or another sulphonyl chloride of the formula R^1SO_2Cl under conditions analogous to

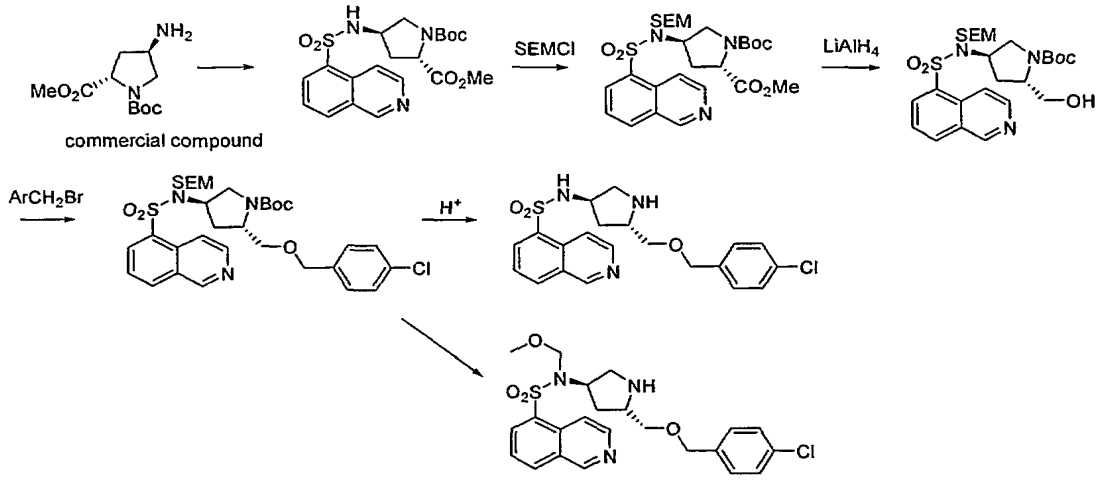
those described above (e.g. in a hydrocarbon solvent such as toluene in the presence of a tertiary amine such as triethylamine or another non-interfering amine).

The ester group of the resulting isoquinolinyl-sulphonyl-piperazinyl ester is then reduced to the corresponding alcohol group using a metal hydride reducing agent such as lithium aluminium hydride in a dry polar solvent such as tetrahydrofuran (THF). The resulting alcohol corresponds to formula (XXII) wherein R^1 is isoquinoline, R^3, R^{3a} and R^4 are each hydrogen, E is $CH\text{-}CH_2$, R^2 and R^5 together form a group CH_2 and X' is OH.

The compound of the formula (XXII) is then treated with chlorobenzyl bromide (or another compound of the formula L-CH (R^6)(R^7)) in the presence of an alkali metal hydride such as sodium hydride. The reaction is typically carried out at room temperature or below, in a polar aprotic solvent such as THF. Removal of the remaining N-benzyl protecting group gives a compound of the formula (I).

Scheme 5 illustrates the preparation of a compound of the formula (I) in which the two nitrogen atoms in the central diamine unit form part of a piperazine ring and where, with reference to formula (I), R^2 and R^5 are linked to form a cyclic structure.

By replacing the dibenzylpiperazine ester intermediate in Scheme 5 with a suitably protected amino-substituted 5-membered cyclic amine such as a 1-N-Boc-4-amino-pyrrolidine-2-carboxylic acid ester, compounds of the formula (I) in which R^3 and R^5 are linked to form a cyclic structure can be prepared. Scheme 6 below illustrates the formation of such a compound of the formula (I) in which the central diamine unit contains a pyrrolidine ring.



Scheme 6

In Scheme 6, 1-N-Boc-4-amino-pyrrolidine-2-carboxylic acid methyl ester is reacted with isoquinolin-5-ylsulphonyl chloride under the conditions described above to form a sulphonamide. A 2-(trimethylsilyl)ethoxymethyl (SEM) group is then introduced at the sulphonamide amine function by reaction with 2-(trimethylsilyl)ethoxymethyl chloride (SEMCl) in the presence of a strong base such as an alkali metal hydride (e.g. NaH) in a polar aprotic solvent such as dimethylformamide (DMF), typically at a reduced temperature. The pendant carboxylic ester moiety is then reduced with lithium aluminium hydride under conditions to those described above in Scheme 4 to give an alcohol which can be reacted with a benzyl halide such as 4-chlorobenzyl bromide or another compound - CH (R^6)(R^7) to give a compound of the formula (I) in which both the nitrogen atoms of the diamine unit (i.e. the sulphonamide nitrogen and the pyrrolidine ring nitrogen) are protected.

The Boc protecting group and the SEM protecting group can both be removed by treatment with acid, e.g. HCl, to give a compound of the formula (I) in which R^2 is hydrogen. Alternatively, the SEM group can be desilylated to give a methoxymethyl group by treatment with acetyl chloride, the Boc group also being removed under the reaction conditions.

Protecting Groups

In many of the reactions described above, it may be necessary to protect one or more groups to prevent reaction from taking place at an undesirable location on the molecule. Examples of protecting groups, and methods of protecting and deprotecting functional groups, can be found in *Protective Groups in Organic Synthesis* (T. Green and P. Wuts; 3rd Edition; John Wiley and Sons, 1999).

A hydroxy group may be protected, for example, as an ether (-OR) or an ester (-OC(=O)R), for example, as: a t-butyl ether; a benzyl, benzhydryl (diphenylmethyl), or trityl (triphenylmethyl) ether; a trimethylsilyl or t-butyldimethylsilyl ether; tetrahydropyranyl (THP) ether or an acetyl ester (-OC(=O)CH_3, -OAc).

An aldehyde or ketone group may be protected, for example, as an acetal (R-$CH(OR)_2$) or ketal ($R_2C(OR)_2$), respectively, in which the carbonyl group (>C=O) is converted to a diether (>$C(OR)_2$), by reaction with, for example, a primary alcohol. The aldehyde or ketone group is readily regenerated by hydrolysis using a large excess of water in the presence of acid.

An amine group may be protected, for example, as an amide (-NRCO-R) or a urethane (-NRCO-OR), for example, as: a methyl amide (-NHCO-CH_3); a benzyloxy amide (-NHCO-$OCH_2C_6H_5$, -NH-Cbz); as a t-butoxy amide (-NHCO-$OC(CH_3)_3$, -NH-Boc); a 2-biphenyl-2-propoxy amide (-NHCO-$OC(CH_3)_2C_6H_4C_6H_5$, -NH-Bpoc), as a 9-fluorenylmethoxy amide (-NH-Fmoc), as a 6-nitroveratryloxy amide (-NH-Nvoc), as a 2-trimethylsilylethyloxy amide (-NH-Teoc), as a 2-(trimethylsilyl)ethoxymethyl (SEM) derivative, as a 2,2,2-trichloroethyloxy amide (-NH-Troc), as an allyloxy amide (-NH-Alloc), as a 2(-phenylsulphonyl)ethyloxy amide (-NH-Psec), or as a benzyl or *para*-methoxybenzyl derivative .

A carboxylic acid group may be protected as an ester for example, as: an C_{1-7} alkyl ester (e.g., a methyl ester; a t-butyl ester); a C_{1-7} haloalkyl ester (e.g., a C_{1-7} trihaloalkyl ester); a triC_{1-7} alkylsilyl-C_{1-7}alkyl ester; or a C_{5-20} aryl-C_{1-7} alkyl ester

(e.g., a benzyl ester; a nitrobenzyl ester); or as an amide, for example, as a methyl amide.

A thiol group may be protected, for example, as a thioether (-SR), for example, as: a benzyl thioether; an acetamidomethyl ether ($-S-CH_2NHC(=O)CH_3$).

Each of the processes described above may include, at any appropriate step, the introduction of a protecting group or the removal of a protecting group as the need arises.

Pharmaceutical Formulations

While it is possible for the active compound to be administered alone, it is preferable to present it as a pharmaceutical composition (e.g. formulation) comprising at least one active compound of the invention together with one or more pharmaceutically acceptable carriers, adjuvants, excipients, diluents, fillers, buffers, stabilisers, preservatives, lubricants, or other materials well known to those skilled in the art and optionally other therapeutic or prophylactic agents.

Thus, the present invention further provides pharmaceutical compositions, as defined above, and methods of making a pharmaceutical composition comprising admixing at least one active compound, as defined above, together with one or more pharmaceutically acceptable carriers, excipients, buffers, adjuvants, stabilizers, or other materials, as described herein.

The term "pharmaceutically acceptable" as used herein pertains to compounds, materials, compositions, and/or dosage forms which are, within the scope of sound medical judgment, suitable for use in contact with the tissues of a subject (e.g. human) without excessive toxicity, irritation, allergic response, or other problem or complication, commensurate with a reasonable benefit/risk ratio. Each carrier, excipient, etc. must also be "acceptable" in the sense of being compatible with the other ingredients of the formulation.

Accordingly, the invention also provides compounds of the formula (I) as defined herein in the form of pharmaceutical compositions.

The pharmaceutical compositions can be in any form suitable for oral, parenteral, topical, intranasal, ophthalmic, otic, rectal, intra-vaginal, or transdermal administration. Where the compositions are intended for parenteral administration, they can be formulated for intravenous, intramuscular, intraperitoneal, or subcutaneous administration or for direct delivery into a target organ or tissue by injection, infusion or other means of delivery.

In one preferred embodiment of the invention, the pharmaceutical composition is in a form suitable for i.v. administration, for example by injection or infusion.

In another preferred embodiment, the pharmaceutical composition is in a form suitable for sub-cutaneous (s.c.) administration.

Pharmaceutical dosage forms suitable for oral administration include tablets, capsules, caplets, pills, lozenges, syrups, solutions, powders, granules, elixirs and suspensions, sublingual tablets, wafers or patches and buccal patches.

Pharmaceutical compositions containing compounds of the formula (I) can be formulated in accordance with known techniques, see for example, Remington's Pharmaceutical Sciences, Mack Publishing Company, Easton, PA, USA.

Thus, tablet compositions can contain a unit dosage of active compound together with an inert diluent or carrier such as a sugar or sugar alcohol, eg; lactose, sucrose, sorbitol or mannitol; and/or a non-sugar derived diluent such as sodium carbonate, calcium phosphate, calcium carbonate, or a cellulose or derivative thereof such as methyl cellulose, ethyl cellulose, hydroxypropyl methyl cellulose, and starches such as corn starch. Tablets may also contain such standard ingredients as binding and granulating agents such as polyvinylpyrrolidone, disintegrants (e.g. swellable crosslinked polymers such as crosslinked carboxymethylcellulose), lubricating agents (e.g. stearates), preservatives (e.g. parabens), antioxidants (e.g. BHT), buffering agents (for example phosphate or citrate buffers), and effervescent agents

such as citrate/bicarbonate mixtures. Such excipients are well known and do not need to be discussed in detail here.

Capsule formulations may be of the hard gelatin or soft gelatin variety and can contain the active component in solid, semi-solid, or liquid form. Gelatin capsules can be formed from animal gelatin or synthetic or plant derived equivalents thereof.

The solid dosage forms (eg; tablets, capsules etc.) can be coated or un-coated, but typically have a coating, for example a protective film coating (e.g. a wax or varnish) or a release controlling coating. The coating (e.g. a Eudragit ™ type polymer) can be designed to release the active component at a desired location within the gastro-intestinal tract. Thus, the coating can be selected so as to degrade under certain pH conditions within the gastrointestinal tract, thereby selectively release the compound in the stomach or in the ileum or duodenum.

Instead of, or in addition to, a coating, the drug can be presented in a solid matrix comprising a release controlling agent, for example a release delaying agent which may be adapted to selectively release the compound under conditions of varying acidity or alkalinity in the gastrointestinal tract. Alternatively, the matrix material or release retarding coating can take the form of an erodible polymer (e.g. a maleic anhydride polymer) which is substantially continuously eroded as the dosage form passes through the gastrointestinal tract.

Compositions for topical use include ointments, creams, sprays, patches, gels, liquid drops and inserts (for example intraocular inserts). Such compositions can be formulated in accordance with known methods.

Compositions for parenteral administration are typically presented as sterile aqueous or oily solutions or fine suspensions, or may be provided in finely divided sterile powder form for making up extemporaneously with sterile water for injection.

Examples of formulations for rectal or intra-vaginal administration include pessaries and suppositories which may be, for example, formed from a shaped mouldable or waxy material containing the active compound.

Compositions for administration by inhalation may take the form of inhalable powder compositions or liquid or powder sprays, and can be administrated in standard form using powder inhaler devices or aerosol dispensing devices. Such devices are well known. For administration by inhalation, the powdered formulations typically comprise the active compound together with an inert solid powdered diluent such as lactose.

The compounds of the inventions will generally be presented in unit dosage form and, as such, will typically contain sufficient compound to provide a desired level of biological activity. For example, a formulation intended for oral administration may contain from 0.1 milligrams to 2 grams of active ingredient, more usually from 10 milligrams to 1 gram, for example, 50 milligrams to 500 milligrams.

The active compound will be administered to a patient in need thereof (for example a human or animal patient) in an amount sufficient to achieve the desired therapeutic effect.

Protein Kinase Inhibitory Activity

The activity of the compounds of the invention as inhibitors of protein kinases A and B can be measured using the assays set forth in the examples below and the level of activity exhibited by a given compound can be defined in terms of the IC50 value. Preferred compounds of the present invention are compounds having an IC50 value of less than 1 micromole, more preferably less than 0.1 micromole.

Therapeutic Uses

Prevention or Treatment of Proliferative Disorders

The compounds of the formula (I) are inhibitors of protein kinase B. As such, they are expected to be useful in providing a means of preventing the growth or inducing

apoptosis of neoplasias. It is therefore anticipated that the compounds will prove useful in treating or preventing proliferative disorders such as cancers. In particular tumours with deletions or inactivating mutations in PTEN may be particularly sensitive to PKB inhibitors. Tumours which have other abnormalities leading to an upregulated PKB pathway signal may also be particularly sensitive to inhibitors of PKB. Examples of such abnormalities include but are not limited to overexpression of one or more PI3K subunits, over-expression of one or more PKB isoforms, or mutations in PI3K, PDK1, or PKB which lead to an increase ion the basal activity of the enzyme in question.

It is also envisaged that the compounds of the invention will be useful in treating other conditions which result from disorders in proliferation or survival such as viral infections, and neurodegenerative diseases for example. PKB plays an important role in maintaining the survival of immune cells during an immune response and therefore PKB inhibitors could be particularly beneficial in immune disorders including autoimmune conditions.

Therefore, PKB inhibitors could be useful in the treatment of diseases in which there is a disorder of proliferation, apoptosis or differentiation.

Examples of cancers which may be inhibited include, but are not limited to, a carcinoma, for example a carcinoma of the bladder, breast, colon (e.g. colorectal carcinomas such as colon adenocarcinoma and colon adenoma), kidney, epidermal, liver, lung, for example adenocarcinoma, small cell lung cancer and non-small cell lung carcinomas, oesophagus, gall bladder, ovary, pancreas e.g. exocrine pancreatic carcinoma, stomach, cervix, thyroid, prostate, or skin, for example squamous cell carcinoma; a hematopoietic tumour of lymphoid lineage, for example leukemia, acute lymphocytic leukemia, B-cell lymphoma, T-cell lymphoma, Hodgkin's lymphoma, non-Hodgkin's lymphoma, hairy cell lymphoma, or Burkett's lymphoma; a hematopoietic tumor of myeloid lineage, for example acute and chronic myelogenous leukemias, myelodysplastic syndrome, or promyelocytic leukemia; thyroid follicular cancer; a tumour of mesenchymal origin, for example fibrosarcoma or habdomyosarcoma, ; a tumor of the central or peripheral nervous

system, for example astrocytoma, neuroblastoma, glioma or schwannoma; melanoma; seminoma; teratocarcinoma; osteosarcoma; xenoderoma pigmentoum; keratoctanthoma; thyroid follicular cancer; or Kaposi's sarcoma.

Thus, in the pharmaceutical compositions, uses or methods of this invention for treating a disease or condition comprising abnormal cell growth, the disease or condition comprising abnormal cell growth in one embodiment is a cancer.

Particular subsets of cancers include breast cancer, ovarian cancer, colon cancer, prostate cancer, oesophageal cancer, squamous cancer and non-small cell lung carcinomas.

It is also possible that some protein kinase B inhibitors can be used in combination with other anticancer agents. For example, it may be beneficial to combine of an inhibitor that induces apoptosis with another agent which acts via a different mechanism to regulate cell growth thus treating two of the characteristic features of cancer development. Examples of such combinations are set out below.

Immune Disorders

Immune disorders for which PKA and PKB inhibitors may be beneficial include but are not limited to autoimmune conditions and chronic inflammatory diseases, for example systemic lupus erythematosus, autoimmune mediated glomerulonephritis, rheumatoid arthritis, psoriasis, inflammatory bowel disease, and autoimmune diabetes mellitus, Eczema hypersensitivity reactions, asthma, COPD, rhinitis, and upper respiratory tract disease.

Other Therapeutic Uses

PKB plays a role in apoptosis, proliferation, differentiation and therefore PKB inhibitors could also be useful in the treatment of the following diseases other than cancer and those associated with immune dysfunction; viral infections, for example herpes virus, pox virus, Epstein-Barr virus, Sindbis virus, adenovirus, HIV, HPV, HCV and HCMV; prevention of AIDS development in HIV-infected individuals;

cardiovascular diseases for example cardiac hypertrophy, restenosis, atherosclerosis; neurodegenerative disorders, for example Alzheimer's disease, AIDS-related dementia, Parkinson's disease, amyotropic lateral sclerosis, retinitis pigmentosa, spinal muscular atropy and cerebellar degeneration; glomerulonephritis; myelodysplastic syndromes, ischemic injury associated myocardial infarctions, stroke and reperfusion injury, degenerative diseases of the musculoskeletal system, for example, osteoporosis and arthritis, aspirin-sensitive rhinosinusitis, cystic fibrosis, multiple sclerosis, kidney diseases.

Methods of Treatment

It is envisaged that the compounds of the formula (I) will useful in the prophylaxis or treatment of a range of disease states or conditions mediated by protein kinase A and/or protein kinase B. Examples of such disease states and conditions are set out above.

Compounds of the formula (I) are generally administered to a subject in need of such administration, for example a human or animal patient, preferably a human.

The compounds will typically be administered in amounts that are therapeutically or prophylactically useful and which generally are non-toxic. However, in certain situations (for example in the case of life threatening diseases), the benefits of administering a compound of the formula (I) may outweigh the disadvantages of any toxic effects or side effects, in which case it may be considered desirable to administer compounds in amounts that are associated with a degree of toxicity.

The compounds may be administered over a prolonged term to maintain beneficial therapeutic effects or may be administered for a short period only. Alternatively they may be administered in a pulsatile manner.

A typical daily dose of the compound can be in the range from 100 picograms to 100 milligrams per kilogram of body weight, more typically 10 nanograms to 10 milligrams per kilogram of bodyweight although higher or lower doses may be administered where required. Ultimately, the quantity of compound administered

will be commensurate with the nature of the disease or physiological condition being treated and will be at the discretion of the physician.

The compounds of the formula (I) can be administered as the sole therapeutic agent or they can be administered in combination therapy with one of more other compounds for treatment of a particular disease state, for example a neoplastic disease such as a cancer as hereinbefore defined. Examples of other therapeutic agents that may be administered together (whether concurrently or at different time intervals) with the compounds of the formula (I) include but are not limited to topoisomerase inhibitors, alkylating agents, antimetabolites, DNA binders and microtubule inhibitors (tubulin targeting agents), such as cisplatin, cyclophosphamide, doxorubicin, irinotecan, fludarabine, 5FU, taxanes, mitomycin C, or radiotherapy. Alternatively, the compounds of the formula (I) can be administered in a combination therapy with monoclonal antibodies or signal transduction inhibitors. For the case of CDK inhibitors combined with other therapies, the two or more treatments may be given in individually varying dose schedules and via different routes.

Where the compound of the formula (I) is administered in combination therapy with one, two, three, four or more other therapeutic agents (preferably one or two, more preferably one), the compounds can be administered simultaneously or sequentially. When administered sequentially, they can be administered at closely spaced intervals (for example over a period of 5-10 minutes) or at longer intervals (for example 1, 2, 3, 4 or more hours apart, or even longer periods apart where required), the precise dosage regimen being commensurate with the properties of the therapeutic agent(s).

The compounds of the invention may also be administered in conjunction with non-chemotherapeutic treatments such as radiotherapy, photodynamic therapy, gene therapy; surgery and controlled diets.

For use in combination therapy with another chemotherapeutic agent, the compound of the formula (I) and one, two, three, four or more other therapeutic

agents can be, for example, formulated together in a dosage form containing two, three, four or more therapeutic agents. In an alternative, the individual therapeutic agents may be formulated separately and presented together in the form of a kit, optionally with instructions for their use.

A person skilled in the art would know through their common general knowledge the dosing regimes and combination therapies to use.

EXPERIMENTAL

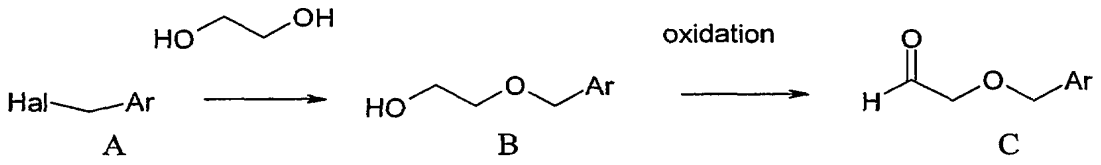
The invention will now be illustrated, but not limited, by reference to the specific embodiments described in the following procedures and examples.

The starting materials for each of the procedures described below are commercially available unless otherwise specified.

GENERAL PREPARATIVE PROCEDURES

Procedure A

General Procedure for Preparation of Aldehyde Intermediates



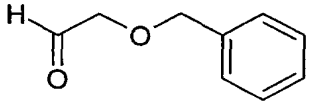
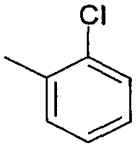
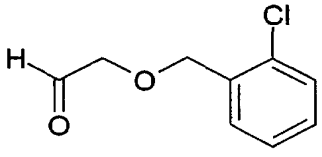
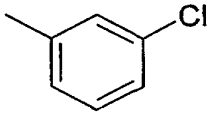
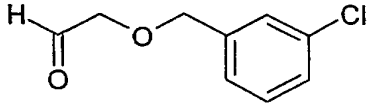
To a slurry of sodium hydride (0.1 mmol) and anhydrous tetrahydrofuran (15 ml) at room temperature was added ethylene glycol (29.8 mmol) during a 10 minute period. The resulting mixture was warmed to 50 °C, then a solution of the arylmethyl halide A (9.8 mmol) in anhydrous tetrahydrofuran (10 ml) was added during a 45 minute period. The mixture was stirred under reflux for 18 h, and then it was allowed to cool to room temperature and partitioned between diethyl ether (20 ml) and water (20 ml). After the separation of the two layers, the organic layer was washed with brine, dried (anhydrous magnesium sulphate), filtered, and evaporated under reduced pressure. The orange oil (2.0 g) thus obtained was purified by flash

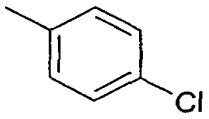
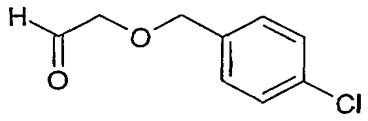
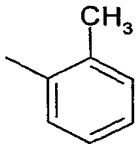
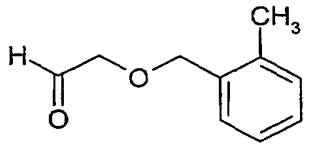
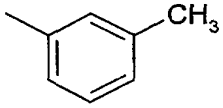
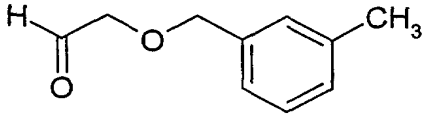
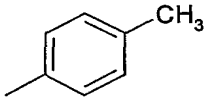
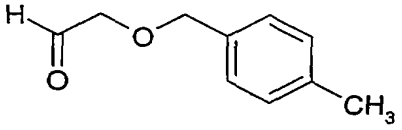
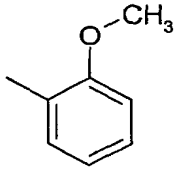
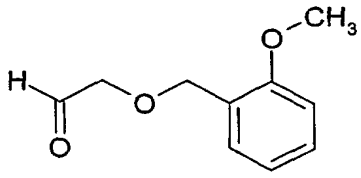
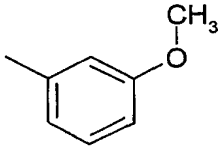
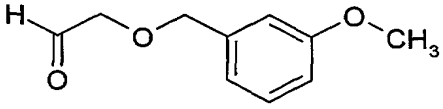
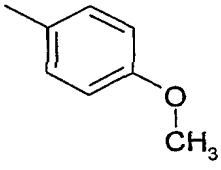
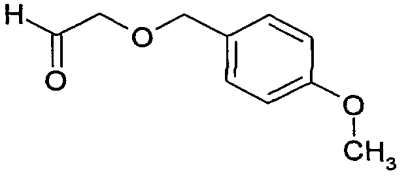
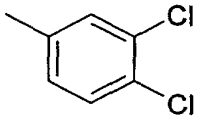
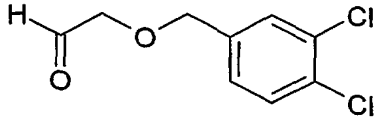
column chromatography on silica using dichloromethane/methanol (v/v; 9:1) as eluent to give the alcohol B as a pale yellow oil (1.5 g, 8 mmol, 82%).

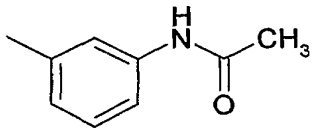
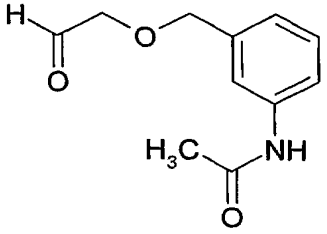
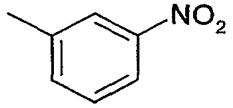
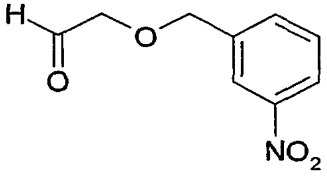
To a solution of the required alcohol (1.46 mmol) in wet dichloromethane (15 ml) Dess-Martin Periodinate (1.60 mmol) was added in one portion. After stirring at room temperature for 2h, the mixture was diluted with a saturated aqueous solution of sodium hydrogen carbonate and sodium thiosulphate (50 ml). After the disappearance of the precipitate (10 min), the mixture was extracted with dichloromethane and the organic phase was then washed with brine, dried (anhydrous magnesium sulphate), filtered, and evaporated under reduced pressure to give the aldehyde as a colourless oil (253 mg, 1.38 mmol, 94%) that was used on Procedure C without any further purification.

By following the procedure described above, the following aldehydes were prepared:

Table A

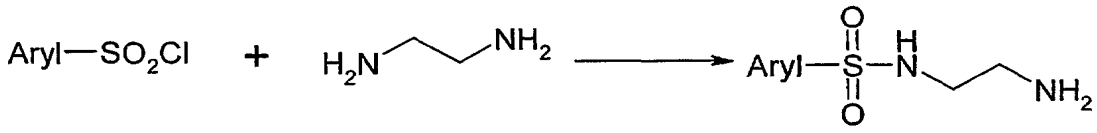
	Starting halide		**Aldehyde**
	Ar	**Hal**	
A1	Aldehyde commercially available		
A2		bromide	
A3		bromide	

A4		bromide	
A5		chloride	
A6		chloride	
A7		chloride	
A8		chloride	
A9		chloride	
A10		chloride	
A11		bromide	

A12		N/A	
A13		bromide	

Procedure B

General Procedure for the Preparation of Sulphonamido-ethylamine Intermediates



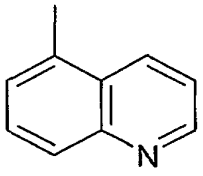
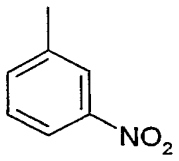
The powdered aryl or heteroaryl sulphonyl chloride (Aryl-SO_2Cl) (1 mmol) was added in small portions to a cooled flask (0 °C) containing the ethylene diamine (10 mmol) in dry dichloromethane (20 ml) with vigorous stirring. The reaction was then stirred for 3 hours at room temperature under a nitrogen atmosphere. After checking its conclusion by TLC, the reaction mixture was extracted with 10% aqueous hydrochloric acid solution. After separation of the two resulting phases, the pH of the aqueous layer was adjusted to 10 with a 10% aqueous sodium hydroxide solution and the aqueous layer was extracted with dichloromethane. The organic layer was then dried (anhydrous magnesium sulphate), filtered and evaporated under reduced pressure to give the aryl-sulphonamido-alkylamine as a solid.

The aryl or heteroaryl sulphonyl chlorides used in the procedure described above were either obtained from commercial sources or were prepared through reaction of

the respective sulphonic acids (2.3 mmol) with thionyl chloride (2.2 ml) in the presence of dimethylformamide (0.3 ml). The reaction was carried out under reflux for 2 hours and, after cooling to room temperature, the reaction mixture was evaporated under reduced pressure to give a solid sulphonyl chloride which was used immediately in the next step.

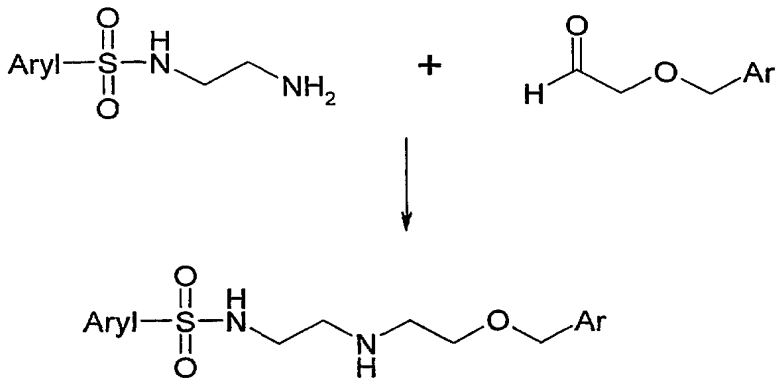
By following the procedure set out above, the following sulphonamido-ethylamines were prepared:

Table B

	Aryl	Characterising Data
B1		^{1}H NMR (CD_3OD, 250 MHz) δ 2.64 (*t*, *J* = 6 Hz, 2H), 2.93 (*t*, *J* = 6 Hz, 2H), 7.85 (*t*, *J* = 8 Hz, 1H), 8.42 (*d*, *J* = 8 Hz, 1H), 8.49 (*d*, *J* = 7 Hz, 1H), 8.58 (*d*, *J* = 6 Hz, 1H), 8.66 (*d*, *J* = 6 Hz, 1H), 9.42 (*s*, 1H); MS (ESI) *m/z* 252.1 [$(M+H)^+$].
B2		MS (ESI) *m/z* 246.2 [$(M+H)^+$]; ^{1}H NMR (DMSO-d_6, 250 MHz) δ 2.50 (*t*, *J* = 6 Hz, 2H), 2.75 (*t*, *J* = 6 Hz, 2H), 7.88 (*t*, *J* = 8 Hz, 1H), 8.19 (*d*, *J* = 8 Hz, 1H), 8.43-8.50 (*m*, 2H).

Procedure C

General Procedure for the Preparation of Compounds of the Formula (I) by Reductive Amination of Sulphonamido-ethylamine Intermediates



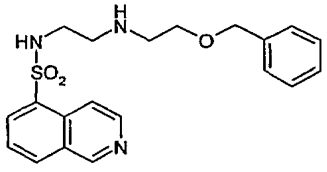
A solution of the aldehyde (0.11 mmol) in 3 ml of dichloroethane was added into a stirred mixture of the amine (27 mg, 0.12 mmol), activated molecular sieves 4Å (30 mg) and 3 ml of 1,2-dichloroethane, at room temperature. The reaction mixture was stirred for 20 minutes at room temperature and then sodium triacetoxyborohydride (0.24 mmol) was added in one portion followed by acetic acid (catalytic amount). The reaction proceeded at room temperature under a nitrogen atmosphere until the reactants were consumed as determined by TLC. The reaction was quenched by adding a saturated solution of $NaHCO_3$, and then the reaction mixture was filtered through a layer of celite. The product was extracted with ethyl acetate, and the combined organic extracts were dried (anhydrous magnesium sulphate), and evaporated till dryness. The crude product was purified by silica column chromatography using dichloromethane/methanol (9.5:0.5) as eluent.

EXAMPLES

Using the synthetic procedures described above, the following compounds of the formula (I) were prepared.

EXAMPLE 1

Isoquinoline-5-sulphonic acid [2-(2-benzyloxy-ethylamino)-ethyl]-amide ($C_{20}H_{23}N_3O_3S$):



Procedure: C

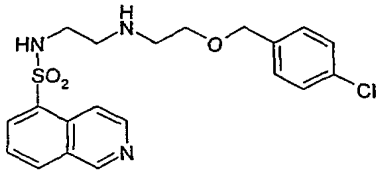
Starting Materials: A1 & B1

Characterising Data:

^{1}H NMR (CD_3OD, 250 MHz) δ 2.72-2.81 (*m*, 4H), 3.08 (*t*, *J* = 6 Hz, 2H), 3.57 (*t*, *J* = 6 Hz, 2H), 4.56 (*s*, 2H), 7.36-7.45 (*m*, 5H), 7.89 (*t*, *J* = 8 Hz, 1H), 8.47 (*d*, *J* = 7 Hz, 1H), 8.55 (*d*, *J* = 7 Hz, 1H), 8.61 (*d*, *J* = 7 Hz, 1H), 8.69 (*d*, *J* = 6 Hz, 1H), 9.46 (*s*, 1H); MS (ESI) *m/z* 386.4 [$(M+H)^+$].

EXAMPLE 2

Isoquinoline-5-sulphonic acid {2-[2-(4-chloro-benzyloxy)-ethylamino]-ethyl}-amide ($C_{20}H_{22}ClN_3O_3S$):



Procedure: C

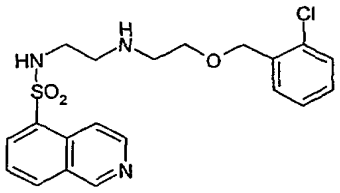
Starting Materials: A4 & B1

Characterising Data:

^{1}H NMR (CD_3OD, 250 MHz) δ 2.69-2.71 (*m*, 4H), 3.03 (*t*, *J* = 6 Hz, 2H), 3.51 (*t*, *J* = 6 Hz, 2H), 4.49 (*s*, 2H), 7.40 (*brs*, 4H), 7.82 (*t*, *J* = 8 Hz, 1H), 8.43 (*d*, *J* = 8 Hz, 1H), 8.51 (*d*, *J* = 8 Hz, 1H), 8.59 (*d*, *J* = 7 Hz, 1H), 8.65 (*d*, *J* = 6 Hz, 1H), 9.42 (*s*, 1H); MS (ESI) *m/z* 420.3 [$(M+H)^+$].

EXAMPLE 3

Isoquinoline-5-sulphonic acid {2-[2-(2-chloro-benzyloxy)-ethylamino]-ethyl}-amide



Procedure: C

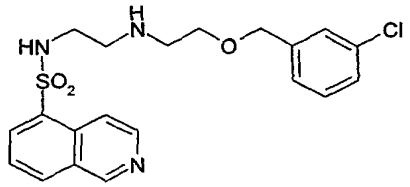
Starting Materials: A2 & B1

Characterising Data:

MS (ESI) *m/z* 420.3 $[(M+H)^+]$; ^1H NMR (CD_3OD, 250 MHz) δ 2.62-2.72 (*m*, 4H), 3.02 (*t*, *J* = 6 Hz, 2H), 3.56 (*t*, *J* = 6 Hz, 2H), 4.49 (*s*, 2H), 7.30-7.53 (*m*, 4H), 7.84 (*t*, *J* = 8 Hz, 1H), 8.41 (*d*, *J* = 8 Hz, 1H), 8.50 (*d*, *J* = 6 Hz, 1H), 8.57 (*d*, *J* = 6 Hz, 1H), 8.63 (*d*, *J* = 6 Hz, 1H), 9.41 (*s*, 1H).

EXAMPLE 4

Isoquinoline-5-sulphonic acid {2-[2-(3-chloro-benzyloxy)-ethylamino]-ethyl}-amide



Procedure: C

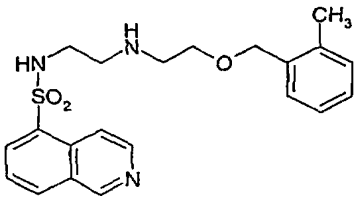
Starting Materials: A3 & B1

Characterising Data:

($C_{20}H_{22}ClN_3O_3S$): MS (ESI) *m/z* 420.3 $[(M+H)^+]$; ^1H NMR (CD_3OD, 250 MHz) δ 2.61-2.69 (*m*, 4H), 3.02 (*t*, *J* = 6 Hz, 2H), 3.49 (*t*, *J* = 6 Hz, 2H), 4.49 (*s*, 2H), 7.29-7.37 (*m*, 4H), 7.84 (*t*, *J* = 8 Hz, 1H), 8.41 (*d*, *J* = 8 Hz, 1H), 8.50 (*dd*, *J* = 7 Hz and *J* = 1 Hz, 1H), 8.58 (*d*, *J* = 6 Hz, 1H), 8.64 (*d*, *J* = 6 Hz, 1H), 9.41 (*s*, 1H).

EXAMPLE 5

Isoquinoline-5-sulphonic acid {2-[2-(2-methyl-benzyloxy)-ethylamino]-ethyl}-amide



Procedure: C

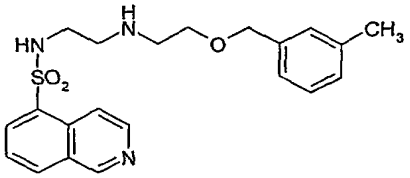
Starting Materials: A5 & B1

Characterising Data:

($C_{21}H_{25}N_3O_3S$): MS (ESI) *m/z* 400.3 [$(M+H)^+$]; ^1H NMR (CD_3OD, 250 MHz) δ 2.34 (*s*, 3H), 2.61-2.69 (*m*, 4H), 3.00 (*t*, *J* = 6 Hz, 2H), 3.51 (*t*, *J* = 6 Hz, 2H), 4.51 (*s*, 2H), 7.15-7.31 (*m*, 4H), 7.83 (*t*, *J* = 8 Hz, 1H), 8.41 (*d*, *J* = 8 Hz, 1H), 8.49 (*d*, *J* = 7 Hz, 1H), 8.56 (*d*, *J* = 6 Hz, 1H), 8.62 (*d*, *J* = 6 Hz, 1H), 9.40 (*s*, 1H).

EXAMPLE 6

Isoquinoline-5-sulphonic acid {2-[2-(3-methyl-benzyloxy)-ethylamino]-ethyl}-amide



Procedure: C

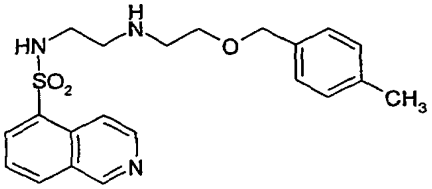
Starting Materials: A6 & B1

Characterising Data:

($C_{21}H_{25}N_3O_3S$): MS (ESI) *m/z* 400.2 [$(M+H)^+$]; ^1H NMR (CD_3OD, 250 MHz) δ 2.36 (*s*, 3H), 2.61-2.69 (*m*, 4H), 3.01 (*t*, *J* = 6 Hz, 2H), 3.48 (*t*, *J* = 6 Hz, 2H), 4.46 (*s*, 2H), 7.14-7.27 (*m*, 4H), 7.84 (*t*, *J* = 8 Hz, 1H), 8.41 (*d*, *J* = 8 Hz, 1H), 8.50 (*d*, *J* = 7 Hz and *J* = 1 Hz, 1H), 8.57 (*d*, *J* = 6 Hz, 1H), 8.63 (*d*, *J* = 6 Hz, 1H), 9.41 (*s*, 1H).

EXAMPLE 7

Isoquinoline-5-sulphonic acid {2-[2-(4-methyl-benzyloxy)-ethylamino]-ethyl}-amide



Procedure: C

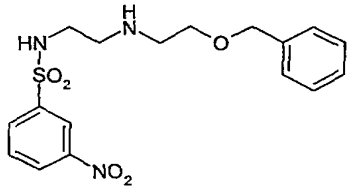
Starting Materials: A7 & B1

Characterising Data:

($C_{21}H_{25}N_3O_3S$): MS (ESI) *m/z* 400.2 [$(M+H)^+$]; ^{1}H NMR (CD_3OD, 250 MHz) δ 2.35 (*s*, 3H), 2.61-2.66 (*m*, 4H), 3.01 (*t*, *J* = 6 Hz, 2H), 3.46 (*t*, *J* = 6 Hz, 2H), 4.44 (*s*, 2H), 7.15-7.25 (*m*, 4H), 7.84 (*t*, *J* = 8 Hz, 1H), 8.41 (*d*, *J* = 8 Hz, 1H), 8.49 (*d*, *J* = 7 Hz and *J* = 1 Hz, 1H), 8.57 (*d*, *J* = 6 Hz, 1H), 8.63 (*d*, *J* = 6 Hz, 1H), 9.41 (*s*, 1H).

EXAMPLE 8

N-[2-(2-Benzyloxy-ethylamino)-ethyl]-3-nitro-benzenesulphonamide



Procedure: C

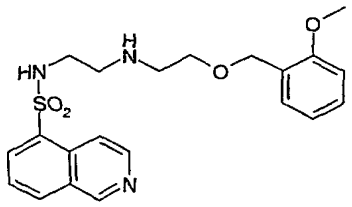
Starting Materials: A1 & B2

Characterising Data:

($C_{17}H_{21}N_3O_5S$): MS (ESI) *m/z* 380.2 [$(M+H)^+$]; ^{1}H NMR (CD_3OD, 250 MHz) δ 2.50 (*t*, *J* = 6 Hz, 2H), 2.75 (*t*, *J* = 6 Hz, 2H), 7.28-7.37 (*m*, 5H), 7.84 (*t*, *J* = 8 Hz, 1H), 8.24 (*d*, *J* = 8 Hz, 1H), 8.49 (*d*, *J* = 7 Hz, 1H), 8.67 (*t*, *J* = 2 Hz, 1H).

EXAMPLE 9

Isoquinoline-5-sulphonic acid {2-[2-(2-methoxy-benzyloxy)-ethylamino]-ethyl}-amide



Procedure: C

Starting Materials: A8 & B1

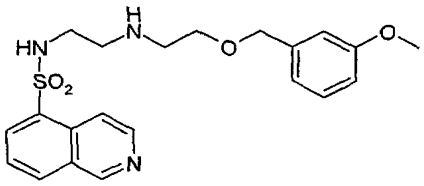
Characterising Data:

($C_{21}H_{25}N_3O_4S$): MS (ESI) *m/z* 416.2 [$(M+H)^+$]; ^{1}H NMR ($CDCl_3$, 250 MHz) δ 2.61 (*t*, J = 5 Hz, 2H), 2.69 (*t*, *J* = 5 Hz, 2H), 3.01 (*t*, *J* = 5 Hz, 2H), 3.50 (*t*, J = 5 Hz, 2H), 3.87 (*s*, 3H), 4.54 (*s*, 2H), 6.92 (*d*, J = 5 Hz, 1H), 6.98 (*t*, J = 7 Hz, 1H) 7.29-

7.35 (*m*, 2H), 7.73 (*t*, J = 7 Hz, 1H), 8.23 (*d*, J = 7 Hz, 1H), 8.46-8.50 (*m*, 2H), 8.71 (*d*, *J* = 5 Hz, 1H), 9.39 (*s*, 1H).

EXAMPLE 10

Isoquinoline-5-sulphonic acid {2-[2-(3-methoxy-benzyloxy)-ethylamino]-ethyl}-amide



Procedure: C

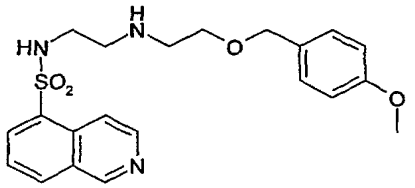
Starting Materials: A9 & B1

Characterising Data:

($C_{21}H_{25}N_3O_4S$): MS (ESI) *m/z* 416.2 [$(M+H)^+$]; ^{1}H NMR ($CDCl_3$, 250 MHz) δ 2.55-2.75 (*m*, 2H), 2.89 (*t*, *J* = 4 Hz, 2H), 2.97 (*t*, *J* = 4 Hz, 2H), 3.30-3.50 (*m*, 2H), 3.67 (*d*, J = 5Hz, 3H), 4.36 (*s*, 2H), 6.73 (*t*, J = 8 Hz, 1H), 6.81 (*t*, J = 6 Hz, 1H) 7.10-7.25 (*m*, 2H), 7.52 (*dt*, J = 4 Hz, 7 Hz, 1H), 8.02 (*dd*, J = 2 Hz, 7 Hz, 1H), 8.24-8.40 (*m*, 2H), 8.48 (*d*, *J* = 5 Hz, 1H), 9.18 (*s*, 1H).

EXAMPLE 11

Isoquinoline-5-sulphonic acid {2-[2-(4-methoxy-benzyloxy)-ethylamino]-ethyl}-amide



Procedure: C

Starting Materials: A10 & B1

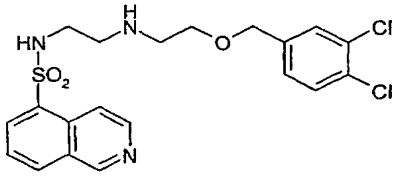
Characterising Data:

($C_{21}H_{25}N_3O_4S$): MS (ESI) *m/z* 416.1 [$(M+H)^+$]; ^{1}H NMR ($CDCl_3$, 250 MHz) δ 2.37 (*t*, J = 5 Hz, 2H), 2.47 (*t*, *J* = 4 Hz, 2H), 2.81 (*t*, *J* = 5 Hz, 2H), 3.23 (*t*, J = 5 Hz, 2H), 3.66 (*s*, 3H), 4.24 (*s*, 2H), 6.72-6.77 (*m*, 2H) 7.06-7.25 (*m*, 2H), 7.55 (*t*, J = 7

Hz, 1H), 8.05 (*d*, J = 8 Hz, 1H), 8.28-8.31 (*m*, 2H), 8.54 (*d*, *J* = 6 Hz, 1H), 9.21 (*s*, 1H).

EXAMPLE 12

Isoquinoline-5-sulphonic acid {2-[2-(3,4-dichloro-benzyloxy)-ethylamino]-ethyl}-amide



Procedure: C

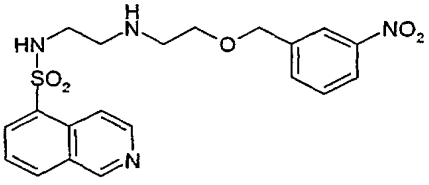
Starting Materials: A11 & B1

Characterising Data:

($C_{20}H_{21}Cl_2N_3O_3S$): MS (ESI) *m/z* 454.06 [$(M+H)^+$]; ^{1}H NMR (CD_3OD, 250 MHz) δ 2.70-2.78 (*m*, 4H), 3.09 (*t*, *J* = 6 Hz, 2H), 3.58 (*t*, *J* = 5 Hz, 2H), 4.55 (*s*, 2H), 7.36 (*dd*, *J* = 8 Hz and *J* = 2 Hz, 1H), 7.57 (*d*, *J* = 8 Hz, 1H), 7.59 (*s*, 1H), 7.91 (*t*, *J* = 8 Hz, 1H), 8.48 (*d*, *J* = 8 Hz, 1H), 8.57 (*dd*, *J* = 8 Hz and *J* = 1 Hz, 1H), 8.64 (*d*, *J* = 8 Hz, 1H), 8.71 (*d*, *J* = 5 Hz, 1H), 9.48 (*s*, 1H).

EXAMPLE 13

Isoquinoline-5-sulphonic acid {2-[2-(3-nitro-benzyloxy)-ethylamino]-ethyl}-amide



Procedure: C

Starting Materials: A13 & B1

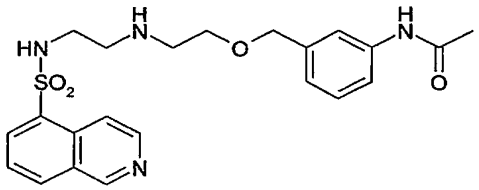
Characterising Data:

($C_{21}H_{25}N_3O_4S$): MS (ESI) *m/z* 431.2 [$(M+H)^+$]; ^{1}H NMR ($CDCl_3$, 250 MHz) δ 2.80 (*t*, J = 5 Hz, 2H), 2.88 (*t*, *J* = 6 Hz, 2H), 3.20 (*t*, *J* = 5 Hz, 2H), 3.67 (*t*, J = 5 Hz,

2H), 4.75 (*s*, 2H), 7.72 (*t*, J = 8 Hz, 1H), 7.82-7.94 (*m*, 2H), 8.33-8.43 (*m*, 3H), 8.63-8.67 (*m*, 2H), 8.88 (*d*, *J* = 6 Hz, 1H), 9.56 (*s*, 1H).

EXAMPLE 14

Isoquinoline-5-sulphonic acid {2-[2-(3-acetamido-benzyloxy)-ethylamino]-ethyl}-amide



14A. [2-(Isoquinoline-5-sulphonylamino)-ethyl]-[2-(3-nitro-benzyloxy)-ethyl]-carbamic acid tert-butyl ester

To a solution of the product of Example 13 (24mg) in dichloromethane (1 ml) was added di-tert-butyl dicarbonate (95 mg). The solution was stirred for 18 hours, after which time, 0.3 g of tris-amine polystyrene resin was added. The solution was stood at room temperature for 4 hours, and then filtered. The filtrate was concentrated to yield the N-Boc protected product, which was subsequently used without further purification.

14B. [2-(Isoquinoline-5-sulphonylamino)-ethyl]-[2-(3-amino-benzyloxy)-ethyl]-carbamic acid tert-butyl ester

The nitro group in the product of Example 14A was reduced to an amino group by the following method. To a solution of the N-Boc protected product of Example 14A in ethanol (1 ml) was added iron powder (20 mg) and a saturated solution of ammonium chloride (1 ml). The mixture was then heated at 80 °C for 30 minutes, and then cooled to room temperature. The mixture was poured into 25 ml of chloroform, and filtered through a plug of Celite®. Concentration of the filtrate yielded the desired title compound, which was subsequently used without further purification.

14C. [2-(3-Acetylamino-benzyloxy)-ethyl]-[2-(isoquinoline-5-sulphonylamino)-ethyl]-carbamic acid tert-butyl ester

The product of Example 14B was acetylated as follows. To a solution of the product of Example 14B in dichloromethane (1ml) was added acetic anhydride (20 µl) and indium triflate (2.6 mg). The solution was stirred for 2 hours at room temperature, then water (2ml) was added, and the mixture stirred for a further hour. Product was extracted with chloroform (3 x 25 ml) and the combined organic extracts were dried and concentrated. Purification of the product by flash column chromatography yielded the title compound.

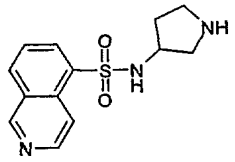
14D. Isoquinoline-5-sulphonic acid {2-[2-(3-acetamido-benzyloxy)-ethylamino]-ethyl}-amide

The Boc protecting group in the product of Example 14A was removed by treating the product with 4N HCl in dioxane, stirring the resulting solution for 16 hours at room temperature, and then concentrating under vacuum. The residue was triturated with diethyl ether (2 x 2 ml) to yield the title compound.

Characterising Data:
($C_{21}H_{25}N_3O_4S$): MS (ESI) *m/z* 431.2 [$(M+H)^+$]; ^{1}H NMR ($CDCl_3$, 250 MHz) δ 2.56 (*t*, J = 5 Hz, 2H), 2.64 (*t*, *J* = 4 Hz, 2H), 2.96 (*t*, *J* = 5 Hz, 2H), 3.45 (*t*, J = 5 Hz, 2H), 3.80 (*s*, 3H) 4.48 (*s*, 2H), 6.83-6.95 (*m*, 2H) 7.22-7.28 (*m*, 2H), 7.66 (*t*, J 7 Hz, 1H), 8.16 (*d*, J 8 Hz, 1H), 8.41 (*d*, J 6 Hz, 2H), 8.65 (*d*, *J* = 6 Hz, 1H), 9.32 (*s*, 1H).

EXAMPLE 15

Isoquinoline-5-sulphonic acid (pyrrolidin-3-yl)-amide

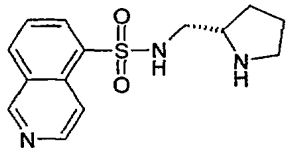


To a solution of isoquinolin-5-ylsulphonyl chloride (100 mg, 0.378 mmol) in water (10 ml) was added $NaHCO_3$ (48 mg, 0.568 mmol) and dichloromethane (30 ml). The organic layer was then separated, dried ($MgSO_4$) and concentrated *in vacuo*.

The residue then taken up in anhydrous dichloromethane (3 ml) and triethylamine (318 µl, 2.270 mmol) was added, followed by 3-amino-pyrrolidine dihydrochloride (181 mg, 1.135 mmol). After stirring at room temperature for 3 hours, the solvent was removed *in vacuo* and the residue was eluted immediately down a flash column without any further work up. Eluting with 10% methanol in dichloromethane afforded the target compound as a white crystalline solid (25 mg, 24%). MS: m/e 278 (M+H). Retention time 0.85 minutes.

EXAMPLE 16

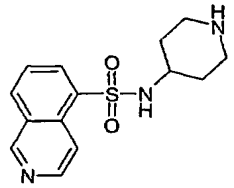
Isoquinoline-5-sulphonic acid (pyrrolidin-2-ylmethyl)-amide



To a solution of isoquinolin-5-ylsulphonyl chloride (100 mg, 0.378 mmol) in water (10 ml) was added $NaHCO_3$ (48 mg, 0.568 mmol) and dichloromethane (30 ml). The organic layer was then separated, dried ($MgSO_4$) and concentrated *in vacuo*. The residue then taken up in anhydrous dichloromethane (3 ml) and (S) – 2-aminomethylpyrrolidine (114 mg, 1.135 mmol) was added. After stirring at room temperature for 3 hours, the solvent was removed *in vacuo* and the residue was eluted immediately down a flash column without any further work up. Eluting with 20% methanol in dichloromethane afforded the target compound as a white crystalline solid (30 mg, 27%). MS: m/e 292 (M+H). Retention time 0.57 minutes.

EXAMPLE 17

Isoquinoline-5-sulphonic acid piperidin-4-ylamide



To a solution of 4-aminopiperidine (0.22 ml, 2.17 mmol) and triethylamine (0.61 ml, 4.4 mmol) in dichloromethane (25 ml) was added in small portions isoquinolin-

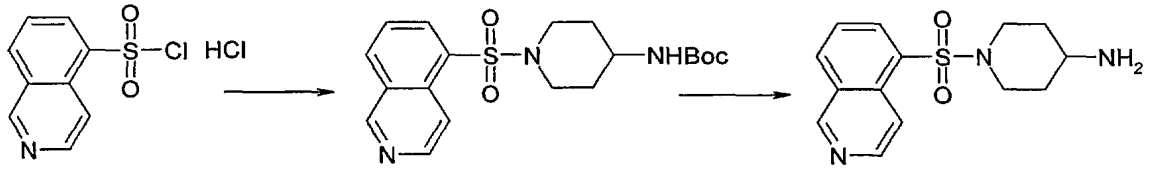
5-ylsulphonyl chloride hydrochloride (498 mg, 2.17 mmol) with stirring and ice-cooling. Water (50 ml) was added to the reaction mixture after stirring overnight. The organic layer was separated and washed twice with water, dried ($MgSO_4$) and concentrated *in vacuo*. The crude product was purified by silica flash column chromatography eluting with 10% methanol in dichloromethane to afford the target compound as a white solid (168 mg, 0.57 mmol, 27%).

Characterising Data:

($C_{14}H_{17}N_3O_2S$): MS (ESI) *m/z* 292.2 [$(M+H)^+$]; ^1H NMR (CD_3OD, 250 MHz) δ 1.30-1.46 (*m*, 2H), 1.88 (*bd*, *J* = 12 Hz, 2H), 2.63-2.74 (*m*, 3H), 3.86 (*bd*, *J* = 12 Hz, 2H), 7.88 (*t*, *J* = 8 Hz, 1H), 8.46 (*d*, *J* = 8 Hz, 1H), 8.46 (*dd*, *J* = 5 Hz and *J* = 1 Hz, 1H), 8.60-8.66 (*m*, 2H), 9.42 (*s*, 1H).

EXAMPLE 18

1-(Isoquinoline-5-sulphonyl)-piperidin-4-ylamine



18A. [1-(Isoquinoline-5-sulphonyl)-piperidin-4-yl]-carbamic acid *tert*-butyl ester

To a solution of 4-(*N*-Boc-amino)-piperidine (891 mg, 4.45 mmol) and triethylamine (0.61 ml, 4.4 mmol) in dichloromethane (30 ml) was added in small portions the isoquinolin-5-ylsulphonyl chloride hydrochloride (494 mg, 2.17 mmol) with stirring and cooling on ice. Water (50 ml) was added to the reaction mixture after stirring overnight. The organic layer was then separated and washed twice with water, dried ($MgSO_4$) and concentrated *in vacuo*. The obtained crude was recrystallised with dichloromethane/hexane to afford the target compound as a white solid (398 mg, 1.02 mmol, 47%).

Characterising Data:

($C_{19}H_{25}N_3O_4S$): ^{1}H NMR ($CDCl_3$, 250 MHz) δ 1.40 (*s*, 9H), 1.86-1.98 (*m*, 4H), 2.67-2.77 (*m*, 2H), 3.40-3.49 (*bs*, 1H), 3.75-3.80 (*m*, 2H), 4.37-4.42 (*bs*, 1H), 7.72 (*t*, *J* = 8 Hz, 1H), 8.23 (*d*, *J* = 8 Hz, 1H), 8.38 (*d*, *J* = 8 Hz, 1H), 8.46 (*d*, *J* = 7 Hz, 1H), 8.68 (*d*, *J* = 6 Hz, 1H), 9.36 (*s*, 1H).

18B. 1-(Isoquinoline-5-sulphonyl)-piperidin-4-ylamine

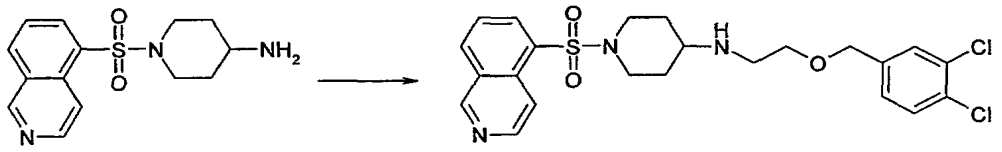
Trifluoroacetic acid (2ml) was added drop wise to a solution of [1-(Isoquinoline-5-sulphonyl)-piperidin-4-yl]-carbamic acid *tert*-butyl ester (309 mg, 0.79 mmol) in dichloromethane (5 ml), with stirring and cooling on ice. After 3h of reaction time the solvents were concentrated *in vacuo*. The crude mixture was dissolved in 20 ml of water and the pH adjusted to 10 with a 1M aqueous solution of NaOH. The aqueous layer was then extracted with ethyl acetate. The obtained organic layer was dried ($MgSO_4$), filtered and evaporated *in vacuo*. The required compound was purified by flash silica column chromatography using 20% methanol in dichloromethane as eluent (61 mg, 0.21 mmol, 26%).

Characterising Data:

($C_{14}H_{17}N_3O_2S$): MS (ESI) *m/z* 292.2 [$(M+H)^+$]; ^{1}H NMR (CD_3OD, 250 MHz) δ 1.53-1.66 (*m*, 2H), 2.01-2.06 (*m*, 2H), 2.71-2.81 (*m*, 2H), 3.05-3.14 (*m*, 1H), 3.97-4.03 (*m*, 2H), 7.91 (*t*, *J* = 8 Hz, 1H), 8.48-8.52 (*m*, 2H), 8.60 (*d*, *J* = 8 Hz, 1H), 8.68 (*d*, *J* = 5 Hz, 1H), 9.45 (*s*, 1H).

EXAMPLE 19

2-(3,4-Dichloro-benzyloxy)-ethyl]-[1-(isoquinoline-5-sulphonyl)-piperidin-4-yl]-amine



A solution of the (3,4-dichloro-benzyloxy)-acetaldehyde (35.1 mg, 0.16 mmol) in 3 ml of dichloroethane was added to a mixture of the amine (47 mg, 0.16 mmol), molecular sieves 4Å (57 mg) and 1,2-dichloroethane (12 ml) under cooling (-5°C)

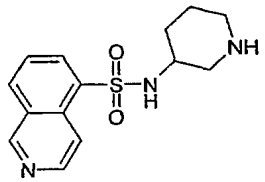
in an ice-salt bath with vigorous stirring. After this mixture was stirred for 20 min sodium triacetoxyborohydride (63 mg, 0.28 mmol) was added in one portion followed by acetic acid (0.2 ml). The reaction proceeded at room temperature under a nitrogen atmosphere until the reactants were consumed as determined by tlc. The reaction was quenched by adding a saturated solution of $NaHCO_3$, followed by filtration through a layer of Celite®. The product was then extracted with ethyl acetate from the filtrate. The obtained organic layer was then dried ($MgSO_4$), filtrated and evaporated *in vacuo*. The resulting compound was purified by flash silica column chromatography using a mixture of dichloromethane/methanol/NH_3 (9:1:0.025) as eluent (38 mg, 0.077 mmol, 48%).

Characterising Data:

($C_{23}H_{25}Cl_2N_3O_3S$): MS (ESI) *m/z* 494.4 $[(M+H)^+]$; ^1H NMR (CD_3OD, 250 MHz) δ 1.33-1.42 (*m*, 2H), 1.94-1.99 (*m*, 2H), 2.47-2.82 (*m*, 5H), 3.57 (*t*, *J* = 5 Hz, 2H), 3.86-3.90 (*m*, 2H), 4.50 (*s*, 2H), 7.27 (*dd*, *J* = 8 Hz and *J* = 2 Hz, 1H), 7.49 (*d*, *J* = 8 Hz, 1H), 7.53 (*d*, *J* = 2 Hz, 1H), 7.90 (*t*, *J* = 8 Hz, 1H), 8.47 (*d*, *J* = 8 Hz, 1H), 8.49 (*dd*, *J* = 8 Hz and *J* = 1 Hz, 1H), 8.65-8.68 (*m*, 2H), 9.44 (*s*, 1H).

EXAMPLE 20

Isoquinoline-5-sulphonic acid piperidin-3-ylamide



To a solution of 3-aminopiperidine dihydrochloride (50 mg, 0.29 mmol) and triethylamine (0.14 ml, 1 mmol) in dichloromethane (5 ml) was added in small portions isoquinolin-5-ylsulphonyl chloride hydrochloride (64 mg, 0.28 mmol) with stirring and ice-cooling. Water (10 ml) was added to the reaction mixture after stirring overnight. The organic layer was separated and washed twice with water, dried ($MgSO_4$) and concentrated *in vacuo*. The crude product was purified by flash silica column eluting with 10% methanol in dichloromethane to afford the target compound as a white solid (71 mg, 0.24 mmol, 86%).

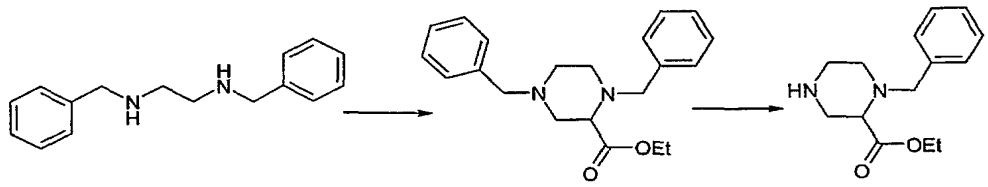
Characterising Data:

($C_{14}H_{17}N_3O_2S$): MS (ESI) *m/z* 292.2 [$(M+H)^+$]; ^{1}H NMR (CD_3OD, 250 MHz) δ 1.13-1.23 (*m*, 1H), 1.47-1.65 (*m*, 1H), 1.75-1.89 (*m*, 2H), 2.41-2.49 (*m*, 1H), 2.64-2.86 (*m*, 2H), 3.59-3.78 (*m*, 2H), 7.88 (*t*, *J* = 8 Hz, 1H), 8.46 (*d*, *J* = 8 Hz, 1H), 8.47 (*dd*, *J* = 5 Hz and *J* = 2 Hz, 1H), 8.62 (*d*, *J* = 8 Hz, 1H), 8.64 (*d*, *J* = 8 Hz, 1H), 9.42 (*s*, 1H).

EXAMPLE 21

5-[3-(4-Chloro-benzyloxymethyl)-piperazine-1-sulphonyl]-isoquinoline

First Part – Preparation 1-benzyl-piperazine-2-carboxylic acid ethyl ester



21A. 1,4-Dibenzyl-piperazine-2-carboxylic acid ethyl ester

To a hot (80°C) stirred solution of *N,N'*-dibenzylethylenediamine (0.98 ml, 4.16 mmol) and triethylamine (1.34 ml, 9.98 mmol) in toluene (5 ml) was added drop wise, but rapidly, ethyl 2,3-dibromopropionate (0.62 ml, 4.3 mmol) in 5ml of toluene. After the addition, the reaction mixture was stirred at 80°C for 3h, then cooled and filtered. The filtrate was washed with saturated aqueous sodium hydrogen carbonate solution (50 ml×2). The organic layer was dried ($MgSO_4$) and the solvent removed *in vacuo* to afford the 1,4-dibenzyl-piperazine-2-carboxylic acid ethyl ester (1.31 g, 3.88mmol, 93%) (*J. Med. Chem*, **1997**, *40*, 3793-3803).

Characterising Data:

($C_{21}H_{26}N_2O_2$): MS (ESI) *m/z* 339.3 [$(M+H)^+$]; ^{1}H NMR ($CDCl_3$, 250 MHz) δ 1.22 (*t*, *J* = 7 Hz, 3H), 2.33-2.75 (*m*, 5H), 3.02-3.05 (*m*, 1H), 3.27-3.31 (*m*, 1H), 3.29-3.92 (*m*, 4H), 4.16 (*q*, *J* = 7 Hz, 2H), 7.24-7.31 (*m*, 10H).

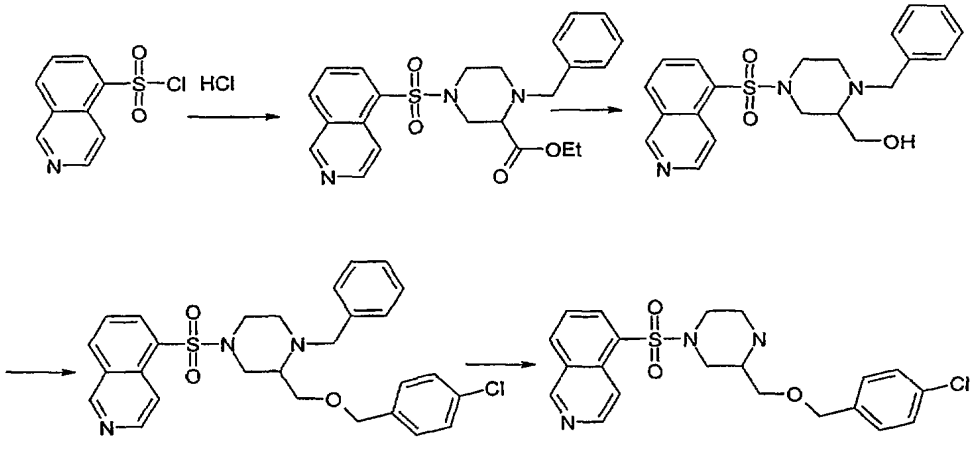
21B. 1-Benzyl-piperazine-2-carboxylic acid ethyl ester

1,4-Dibenzyl-piperazine-2-carboxylic acid ethyl ester (810 mg, 2.43 mmol) was dissolved in 1,2-dichloroethane (8 ml) and cooled in an ice bath at (0°C). A solution of 1-chloroethyl carbono chloridate (0.29 ml, 2.66 mmol) in 1,2-dichloroethane (4 ml) was then added drop wise over 10 min and stirring was continued at 0°C for 10 min. The mixture was refluxed for 1h, cooled to rt and the solvents were evaporated *in vacuo*. The crude oil residue was dissolved in methanol (4 ml) and refluxed for 1h. The solvent was evaporated again and the crude was dissolved in water (15 ml). The aqueous phase was extracted with diethyl ether followed by dichloromethane. The pH of the remaining aqueous phase was adjusted to 9, adding solid sodium hydrogen carbonate, and extracted with dichloromethane. This organic layer was dried (MgSO4), filtered and evaporated *in vacuo* to afford the 1-benzyl-piperazine-2-carboxylic acid ethyl ester as an oil (398 mg, 1.6 mmol, 66%). (*Synthesis*, **1991**, 318-320).

Characterising Data:

($C_{14}H_{20}N_2O_2$): MS (ESI) *m/z* 249.2 [$(M+H)^+$]; ^{1}H NMR ($CDCl_3$, 250 MHz) δ 1.23 (*t*, *J* = 7 Hz, 3H), 1.68 (*brs*, 1H), 2.17-2.24 (*m*, 1H), 2.72-2.91 (*m*, 3H), 3.02-3.15 (*m*, 3H), 3.60 (*dd*, *J* = 68 Hz and *J* = 13 Hz, 2H), 4.15 (*q*, *J* = 7 Hz, 2H), 7.15-7.26 (*m*, 5H).

Second Part – Preparation of 5-[3-(4-chloro-benzyloxymethyl)-piperazine-1-sulphonyl]-isoquinoline



21C. 1-Benzyl-4-(isoquinoline-5-sulphonyl)-piperazine-2-carboxylic acid ethyl ester.

To a solution of 1-benzyl-piperazine-2-carboxylic acid ethyl ester (60 mg, 0.24 mmol) and triethylamine (0.09 ml, 0.69 mmol) in dichloromethane (10 ml) was added in small portions the isoquinolin-5-ylsulphonyl chloride hydrochloride (60 mg, 0.26 mmol) with stirring and cooling on ice. Water (10 ml) was added to the reaction mixture after 2h45 min reaction time. The organic layer was then separated and washed twice with water and once with brine, dried ($MgSO_4$) and concentrated *in vacuo*. The obtained crude was purified by silica flash column chromatography eluting with 4% methanol in dichloromethane to afford the target compound (61 mg, 0.14 mmol, 57%).

Characterising Data:
($C_{23}H_{25}N_3O_4S$): MS (ESI) *m/z* 440.3 [$(M+H)^+$]; ^{1}H NMR ($CDCl_3$, 250 MHz) δ 1.20 (*t*, *J* = 7 Hz, 3H), 2.48-2.56 (*m*, 1H), 2.99-3.45 (*m*, 5H), 3.61-3.70 (*m*, 2H), 3.88-4.11 (*m*, 3H), 7.23-7.32 (*m*, 5H), 7.74 (*t*, *J* = 8 Hz, 1H), 8.26 (*d*, *J* = 8 Hz, 1H), 8.40 (*dd*, *J* = 8 Hz and *J* = 1 Hz, 1H), 8.47 (*d*, *J* = 6 Hz, 1H), 8.70 (*d*, *J* = 6 Hz, 1H), 9.38 (*s*, 1H).

21D. [1-Benzyl-4-(isoquinoline-5-sulphonyl)-piperazin-2-yl]-methanol

A solution of 1-benzyl-4-(isoquinoline-5-sulphonyl)-piperazine-2-carboxylic acid ethyl ester (193 mg, 0.44 mmol) in tetrahydrofuran (2 ml) was added to a stirred suspension of lithium aluminium hydride (0.45 ml, 0.45 mmol) on ice cooling. The reaction mixture was stirred for 1h30 min. 30 µl of water followed by 40 µl of 1M aqueous solution of sodium hydroxide were added to the reaction mixture and left stirring overnight. Water (30 µl) was then added and the resulting suspension was filtered through a layer of Celite and washed with diethyl ether. The ether phase was evaporated *in vacuo* and the obtained crude product was purified by flash silica column chromatography using 10% methanol in dichloromethane as eluent to afford the [1-benzyl-4-(isoquinoline-5-sulphonyl)-piperazin-2-yl]-methanol (116 mg, 0.29 mmol, 66%).

Characterising Data:

($C_{21}H_{23}N_3O_3S$): MS (ESI) *m/z* 398.2 [$(M+H)^+$]; ^{1}H NMR ($CDCl_3$, 250 MHz) δ 2.20 (*s*, 1H), 2.41-2.50 (*m*, 1H), 2.72-2.73 (*m*, 1H), 2.86-2.96 (*m*, 2H), 3.04-3.12 (*m*, 1H), 3.37-3.65 (*m*, 3H), 3.63-3.84 (*m*, 1H), 3.92-4.06 (*m*, 2H), 7.24-7.35 (*m*, 5H), 7.75 (*t*, *J* = 8 Hz, 1H), 8.26 (*d*, *J* = 8 Hz, 1H), 8.40 (*dd*, *J* = 8 Hz and *J* = 1 Hz, 1H), 8.53 (*d*, *J* = 6 Hz, 1H), 8.70 (*d*, *J* = 8 Hz, 1H), 9.39 (*s*, 1H).

21E. 5-[4-Benzyl-3-(4-chloro-benzyloxymethyl)-piperazine-1-sulphonyl]-isoquinoline

Sodium hydride (27 mg, 60% mixture in oil, 0.67 mmol) was added to a suspension of [1-benzyl-4-(isoquinoline-5-sulphonyl)-piperazin-2-yl]-methanol (130 mg, 0.33 mmol) in dimethylformamide (5 ml) and this mixture was stirred for 15 min followed by addition of 4-chlorobenzyl bromide (64mg, 0.31 mmol). After 4h30 min the solution was diluted with water (20 ml) and extracted with ethyl acetate. The organic layer was washed with water and the solvent was removed *in vacuo*. The obtained crude was purified by flash silica column chromatography using 10% methanol in dichloromethane as eluent to afford the 5-[4-benzyl-3-(4-chloro-benzyloxymethyl)-piperazine-1-sulphonyl]-isoquinoline (84 mg, 0.16 mmol, 52%).

Characterising Data:

($C_{28}H_{28}ClN_3O_3S$): MS (ESI) *m/z* 522.32 [$(M+H)^+$]; ^{1}H NMR ($CDCl_3$, 250 MHz) δ 2.32-2.46 (*m*, 1H), 2.67-2.84 (*m*, 2H), 3.06-3.93 (*m*, 8H), 4.31 (*brs*, 2H), 7.16-7.33 (*m*, 9H), 7.70 (*t*, *J* = 8 Hz, 1H), 8.20 (*d*, *J* = 8 Hz, 1H), 8.36 (*d*, *J* = 7 Hz, 1H), 8.52 (*brs*, 1H), 8.67 (*d*, *J* = 6 Hz, 1H), 9.34 (*s*, 1H).

21F. 5-[3-(4-Chloro-benzyloxymethyl)-piperazine-1-sulphonyl]-isoquinoline

5-[4-Benzyl-3-(4-chloro-benzyloxymethyl)-piperazine-1-sulphonyl]-isoquinoline (84 mg, 0.16 mmol) was dissolved in 1,2-dichloroethane (4 ml) and cooled in an ice bath at (0 °C). A solution of 1-chloroethyl carbonochloridate (0.04 ml, 0.38 mmol) in 1,2-dichloroethane (2 ml) was then added drop wise over 10 min and stirring was continued at 0°C for 10 min. The mixture was refluxed for 3 days, cooled to rt and the solvents were evaporated *in vacuo*. The crude oil residue was dissolved in

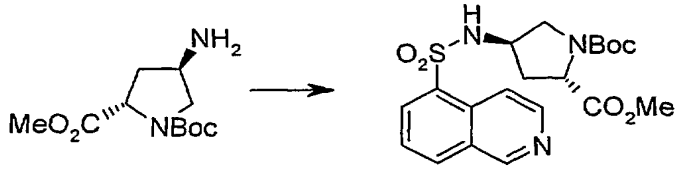
methanol (5 ml) and refluxed for 2h. The solvent was evaporated again and the crude was dissolved in water (10 ml). The aqueous phase was then extracted with diethyl ether followed by dichloromethane. The pH of the remaining aqueous phase is the adjusted to 9, adding solid sodium hydrogen carbonate, and extracted with dichloromethane. This organic layer was dried ($MgSO_4$) filtered and evaporated *in vacuo*. The obtained crude was purified by flash silica column chromatography using 10% methanol in dichloromethane to afford the 5-[3-(4-chloro-benzyloxymethyl)-piperazine-1-sulphonyl]-isoquinoline (29 mg, 0.07 mmol, 42%).

Characterising Data:
($C_{21}H_{22}ClN_3O_3S$): MS (ESI) *m/z* 432.19 [$(M+H)^+$]; ^1H NMR ($CDCl_3$, 250 MHz) δ 2.35-2.46 (*m*, 1H), 2.67-3.63 (*m*, 9H), 4.41 (*s*, 2H), 7.20 (*d*, *J* = 8 Hz, 2H), 7.30 (*d*, *J* = 8 Hz, 2H), 7.72 (*t*, *J* = 8 Hz, 1H), 8.23 (*d*, *J* = 7 Hz, 1H), 8.36 (*d*, *J* = 8 Hz, 1H), 8.50 (*d*, *J* = 6 Hz, 1H), 8.68 (*d*, *J* = 6 Hz, 1H), 9.35 (*s*, 1H).

EXAMPLE 22

Isoquinoline-5-sulphonic acid [5-(S)-(4-chlorobenzyloxymethyl)pyrrolidin-3-(R)-yl]methoxymethyl amide

22A. 4-(R)-(Isoquinoline-5-sulphonylamino)pyrrolidine-1,2-(S)-dicarboxylic acid 1-*tert*-butyl ester 2-methyl ester

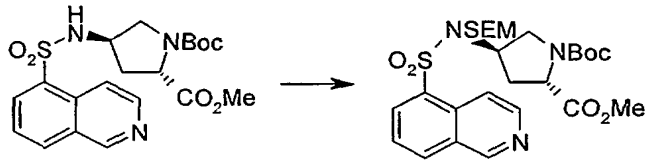


To a suspension of isoquinoline-5-sulphonic acid (237 mg, 1.133 mmol) in thionyl chloride (1.1 ml) was added DMF (20 µl) and the mixture refluxed for 3 h. The resulting precipitate was cooled, concentrated and used as the crude hydrochloride salt.

To a solution of the hydrochloride salt of the Boc-protected pyrrolidine derivative shown above (265 mg, 0.944 mmol) in DCM (9 ml) at rt was added triethylamine

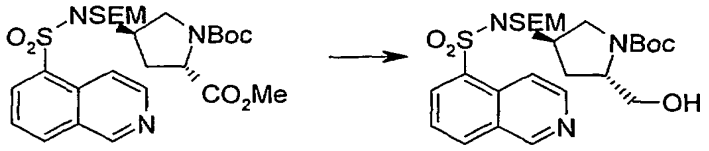
(658 µl, 4.720 mmol) and DMAP (20 mg, 0.164 mmol). The crude sulphonyl chloride prepared above was added in one portion and the resulting mixture stirred for 1 h. Brine (20 ml) was added, the phases separated and the aqueous further extracted with DCM (3 x 15 ml). Organic phases were combined, dried ($MgSO_4$), concentrated and the crude purified by silica column chromatography (5% MeOH/DCM) to give the desired product as an oil (309 mg, 63%). ^1H NMR ($CDCl_3$) δ 1.27 (9H, s), 1.81-2.24 (2H, m), 2.90-3.12 (1H, m), 3.37-3.50 (1H, m), 3.62 (3H, s), 3.77-3.94 (1H, m), 4.10-4.27 (1H, m), 5.91-6.27 (1H, m), 7.60-7.68 (1H, m), 8.15-8.18 (1H, m), 8.31-8.41 (2H, m), 8.55-8.62 (1H, m), 9.30 (1H, s).

22B. 4-(R)-[Isoquinoline-5-sulphonyl)-(2-trimethylsilanylethoxymethyl)amino]pyrrolidine-1,2-(S)-dicarboxylic acid 1-*tert*-butyl ester 2-methyl ester



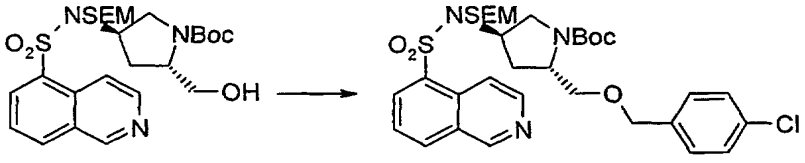
To a solution of N-Boc protected pyrrolidine sulphonamide shown above (357 mg, 0.820 mmol) in DMF (8.1 ml) at 0 °C was added NaH (42.7 mg of a 60% dispersion in mineral oil, 1.066 mmol) in one portion. After 5 min, SEMCl (152 µl) was added and stirring continued for 5 min. Water (30 ml) was added and the aqueous extracted with ethyl acetate (3 x 30 ml). Organic phases were combined, dried ($MgSO_4$), concentrated and the crude purified by silica column chromatography (70% EtOAc/pet ether) to give the desired product as an oil (372 mg, 80%).^1H NMR ($CDCl_3$) δ 0.00 (9H, s), 0.80-0.88 (2H, m), 1.37, 1.42 (9H, 2 x s), 1.85-2.55 (2H, m), 3.26-3.37 (1H, m), 3.52-3.62 (3H, m), 3.69 (3H, s), 4.28-4.49 (2H, m), 4.87-5.04 (2H, m), 7.68-7.74 (1H, m), 8.22-8.46 (3H, m), 8.69-8.71 (1H, m), 9.37 (1H, s).

22C. 2-(S)-Hydroxymethyl-4-(R)-[isoquinoline-5-sulphonyl)-(2-trimethylsilanylethoxymethyl)amino]pyrrolidine-1-carboxylic acid *tert*-butyl ester



To a solution of the ester shown above (330 mg, 0.584 mmol) in THF (10 ml) at 0 °C was added $LiAlH_4$ (584 µl of a 1 M sol in THF, 0.584 mmol). After 20 min, more $LiAlH_4$ (300 µl, 0.300 mmol) was added, then after a further 20 min a third portion of $LiAlH_4$ (200 µl, 0.200 mmol). The reaction was then diluted with diethyl ether (20 ml) and quenched by the dropwise addition of water (40 µl), followed by 10% NaOH (40 µl). After stirring overnight, water (120 µl) was added dropwise and the resulting white precipitate filtered off through celite. The filtrate was concentrated and the crude purified by silica column chromatography (EtOAc) to give the desired product as an oil (227 mg, 72%).^{1}H NMR ($CDCl_3$) δ 0.00 (9H, s), 0.81-0.87 (2H, m), 1.44 (9H, s), 1.85-2.30 (2H, m), 3.30-4.50 (8H, m), 4.87-5.04 (2H, m), 7.69-7.75 (1H, m), 8.22-8.26 (1H, m), 8.35-8.37 (1H, m), 8.44-8.47 (1H, m), 8.70-8.72 (1H, m), 9.38 (1H, s).

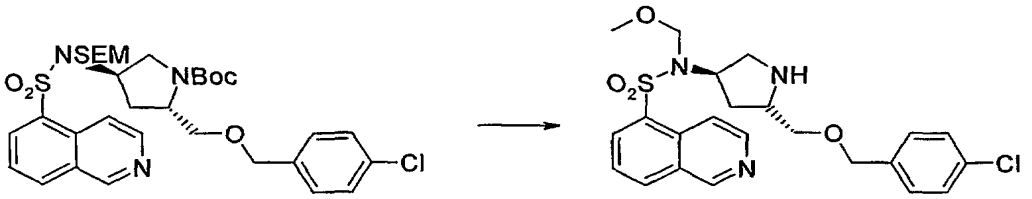
22D. 2-(S)-(4-Chlorobenzyloxymethyl)-4-(R)-[isoquinoline-5-sulphonyl)-(2-trimethylsilanylethoxymethyl)amino]pyrrolidine-1-carboxylic acid *tert*-butyl ester



To a solution of the alcohol shown above (113 mg, 0.210 mmol) in DMF (2.1 ml) at 0 °C was added NaH (10.1 mg of a 60% dispersion in mineral oil, 0.252 mmol). After 1 h, 4-chlorobenzyl bromide (45 mg, 0.221 mmol) was added and the mixture warmed to rt. After 15 h, brine (20 ml) was added and the aqueous layer extracted with diethyl ether (5 x 10 ml). Organic layers were combined, dried ($MgSO_4$), concentrated and the crude purified by silica column chromatography (70% EtOAc/pet ether) to give the desired product as an oil (92 mg, 66%).^{1}H NMR ($CDCl_3$) □ 0.00 (9H, s), 0.82-0.88 (2H, m), 1.41 (9H, s), 1.80-2.35 (2H, m), 3.21-

4.05 (7H, m), 4.38 (2H, s), 4.52-4.63 (1H, m), 4.90-5.05 (2H, m), 7.16-7.32 (4H, m), 7.52-7.58 (1H, m), 8.16-8.19 (1H, m), 8.30-8.36 (2H, m), 8.65-8.68 (1H, m), 9.35 (1H, s).

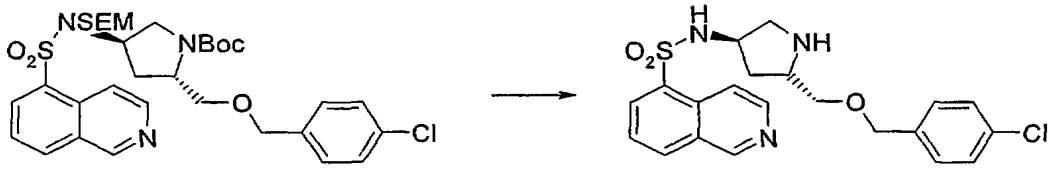
22E. Isoquinoline-5-sulphonic acid [5-(S)-(4-chlorobenzyloxymethyl)pyrrolidin-3-(R)-yl]methoxymethyl amide



To a solution of the N-Boc protected pyrrolidine sulphonamide shown above (55 mg, 0.0830 mmol) in methanol (2 ml) at 0 °C was added acetyl chloride (295 µl). After stirring for 4 h at rt, the solution was concentrated and purified by NH_2 Isolute column (washing with 2:1 MeCN/MeOH) to give the desired product as an oil (36 mg, 92%). ^{1}H NMR ($CDCl_3$) δ 1.57-2.00 (2H, m), 2.82-3.07 (2H, m), 3.24-3.43 (3H, m), 3.38 (3H, s), 4.21-4.27 (1H, m), 4.43 (2H, s), 4.92 (1H, d), 5.02 (1H, d), 7.18-7.33 (4H, m), 7.65-7.71 (1H, m), 8.20-8.23 (1H, m), 8.32-8.34 (1H, m), 8.42-8.45 (1H, m), 8.68-8.71 (1H, m), 9.36 (1H, s). LC/MS: R_t 6.40 $[M+H]^+$ 476.

EXAMPLE 23

Isoquinoline-5-sulphonic acid [5-(S)-(4-chlorobenzyloxymethyl)pyrrolidin-3-(R)-yl] amide



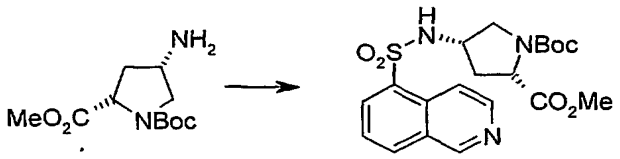
To a solution of the sulphonamide of Example 22D (22 mg, 0.0462 mmol) in MeOH (1 ml) at rt was added 6M HCl (1 ml). After refluxing for 4 h, the solution was cooled, concentrated and purified by NH_2 Isolute column (washing with MeOH) to give the desired product as an oil (15 mg, 75%). ^{1}H NMR ($CDCl_3$) δ

1.48-1.57 (2H, m), 2.51 (1H, dd), 2.91 (1H, dd), 3.11-3.34 (3H, m), 3.66-3.75 (1H, m), 4.33 (2H, s), 7.08-7.25 (4H, m), 7.44-7.47 (1H, m), 8.13-8.16 (1H, m), 8.31-8.40 (2H, m), 8.59-8.61 (1H, m), 9.30 (1H, s). LC/MS: R_t 6.00 $[M+H]^+$ 432.

EXAMPLE 24

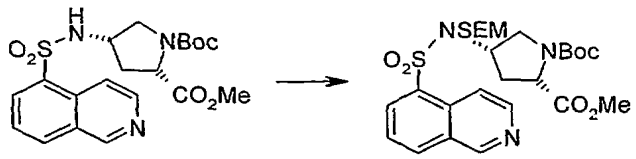
Isoquinoline-5-sulphonic acid [5-(S)-(4-chlorobenzyloxymethyl)pyrrolidin-3-(S)-yl] amide

24A. 4-(S)-(Isoquinoline-5-sulphonylamino)pyrrolidine-1,2-(S)-dicarboxylic acid 1-*tert*-butyl ester 2-methyl ester



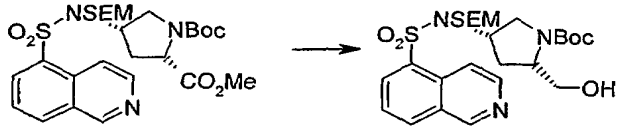
To a solution of the N-Boc protected pyrrolidine amine shown above (948 mg, 3.881 mmol) in DCM (40 ml) at 0 °C was added triethylamine (2.7 ml, 19.405 mmol) and DMAP (47 mg, 0.388 mmol). Isoquinoline-5-sulphonyl chloride hydrochloride (1.021 g, 3.881 mmol) was added in one portion and the resulting solution warmed to rt and stirred for 18 h. Saturated $NaHCO_3$ (40 ml) was added and the aqueous layer extracted with DCM (3 x 40 ml). Organic layers were combined, dried ($MgSO_4$), concentrated and the crude purified by silica column chromatography (EtOAc) to give the desired product as an oil (1.278 g, 76%). ^1H NMR ($CDCl_3$) δ 1.31, 1.34 (9H, 2 x s), 1.64-1.82 (1H, m), 2.10-2.38 (1H, m), 3.24-3.35 (2H, m), 3.73 (3H, s), 3.95-4.22 (2H, m), 6.35-6.65 (1H, m), 7.71-7.76 (1H, m), 8.24-8.27 (1H, m), 8.37-8.41 (1H, m), 8.46-8.49 (1H, m), 8.74-8.79 (1H, m), 9.40 (1H, s).

24B. 4-(S)-[Isoquinoline-5-sulphonyl)-(2-trimethylsilanylethoxymethyl)amino]pyrrolidine-1,2-(S)-dicarboxylic acid 1-*tert*-butyl ester 2-methyl ester



To a solution of the N-unsubstituted sulphonamide shown above (1.278 g, 2.934 mmol) in DMF (29 ml) at 0 °C was added NaH (153 mg of a 60% dispersion in mineral oil, 3.815 mmol) in one portion. After 10 min, SEMCl (545 µl, 3.081 mmol) was added and stirring continued for 30 min. Water (100 ml) was added and the aqueous extracted with ethyl acetate (3 x 50 ml). The organic phases were combined, dried ($MgSO_4$), concentrated and the crude product purified by silica column chromatography (EtOAc) to give the title compound as an oil (1.225 g, 74%).^{1}H NMR ($CDCl_3$) □ 0.00 (9H, s), 0.80-0.87 (2H, m), 1.44, 1.39 (9H, 2 x s), 2.00-2.50 (2H, m), 3.37 (1H, t), 3.52-3.67 (3H, m), 3.74 (3H, s), 4.10-4.28 (2H, m), 4.99 (2H, s), 7.70-7.77 (1H, m), 8.25-8.28 (1H, m), 8.34-8.39 (1H, m), 8.46-8.49 (1H, m), 8.72-8.74 (1H, m), 9.39 (1H, s).

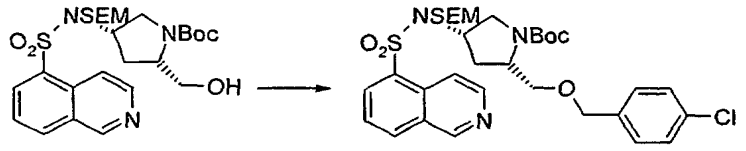
24C. 2-(S)-Hydroxymethyl-4-(S)-[isoquinoline-5-sulphonyl)-(2-trimethylsilanylethoxymethyl)amino]pyrrolidine-1-carboxylic acid *tert*-butyl ester



To a solution of the ester shown above (1.225 g, 2.167 mmol) in THF (35 ml) at 0 °C was added $LiAlH_4$ (2.20 ml of a 1 M sol in THF, 2.20 mmol). After 20 min, more $LiAlH_4$ (2.20 ml, 2.20 mmol) was added, then after a further 20 min a third portion of $LiAlH_4$ (2.20 ml, 2.20 mmol). The reaction was then quenched by the dropwise addition of water (290 µl), followed by 10% NaOH (290 µl). After stirring overnight, water (870 µl) was added dropwise and the resulting white precipitate filtered off through Celite. The filtrate was concentrated and the crude purified by silica column chromatography (EtOAc) to give the desired product as an oil (454 mg, 39%).^{1}H NMR ($CDCl_3$) δ 0.00 (9H, s), 0.81-0.87 (2H, m), 1.45 (9H, s), 1.5-2.1

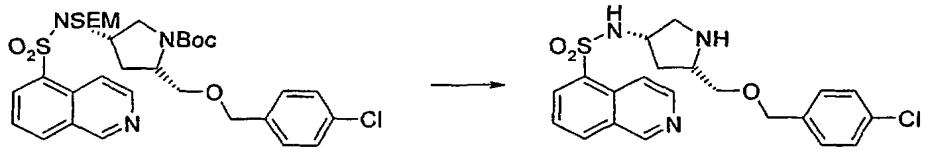
(2H, m), 3.19 (1H, t), 3.53-4.20 (7H, m), 4.97 (2H, s), 7.70-7.77 (1H, m), 8.24-8.27 (1H, m), 8.34-8.37 (1H, m), 8.45-8.49 (1H, m), 8.72-8.74 (1H, m), 9.39 (1H, s).

24D. 2-(S)-(4-Chlorobenzyloxymethyl)-4-(S)-[isoquinoline-5-sulphonyl)-(2-trimethylsilanylethoxymethyl)amino]pyrrolidine-1-carboxylic acid *tert*-butyl ester



To a solution of the alcohol shown above (454 mg, 0.844 mmol) in DMF (8.4 ml) at 0 °C was added NaH (41 mg of a 60% dispersion in mineral oil, 1.013 mmol). After 1 h, 4-chlorobenzyl bromide (182 mg, 0.886 mmol) was added and the mixture warmed to rt. After 15 h, water (150 ml) was added and the aqueous layer extracted with diethyl ether (3 x 40 ml). Organic layers were combined, dried ($MgSO_4$), concentrated and the crude purified by silica column chromatography (EtOAc) to give the desired product as an oil (223 mg, 40%). ^{1}H NMR ($CDCl_3$) δ 0.00 (9H, s), 0.80-0.84 (2H, m), 1.43 (9H, s), 1.8-2.3 (2H, m), 3.20 (1H, t), 3.48-3.93 (6H, m), 4.10-4.22 (1H, m), 4.48 (2H, s), 4.92-5.08 (2H, m), 7.22-7.34 (4H, m), 7.74-7.80 (1H, m), 8.27-8.30 (1H, m), 8.46-8.53 (2H, m), 8.72-8.74 (1H, m), 9.42 (1H, s).

24E. Isoquinoline-5-sulphonic acid [5-(S)-(4-chlorobenzyloxymethyl)pyrrolidin-3-(S)-yl] amide



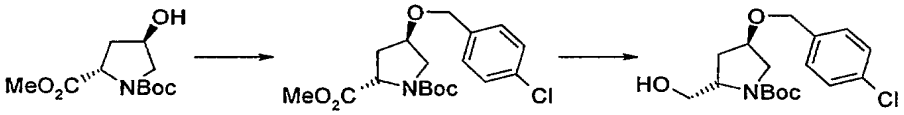
To a solution of the N-Boc protected pyrrolidine sulphonamide shown above (110 mg, 0.1661 mmol) in MeOH (5 ml) at rt was added 6M HCl (5 ml). After refluxing for 4 h, the solution was cooled, concentrated and purified by SCX-2 Isolute column (washing with MeOH, then 1 M NH_3 in MeOH). The desired fractions were combined, concentrated and passed through a small plug of silica, eluting with

10%MeOH in DCM, with the filtrate concentrated to give the desired product as an oil (53 mg, 74%).^{1}H NMR ($CDCl_3$) δ 1.25-1.43 (1H, m), 1.97-2.10 (1H, m), 2.67-2.80 (2H, m), 3.27-3.56 (3H, m), 3.79-3.84 (1H, m), 4.51 (1H, d), 4.58 (1H, d), (7.29-7.40 (4H, m), 7.66-7.73 (1H, m), 8.15-8.22 (2H, m), 8.40-8.43 (1H, m), 8.58-8.60 (1H, m), 9.36 (1H, d). LC/MS: R_t 4.57 $[M+H]^+$ 432.

EXAMPLE 25

Isoquinoline-5-sulphonic acid [4-(R)-(4-chlorobenzyloxy)pyrrolidin-2-(S)-ylmethyl]amide

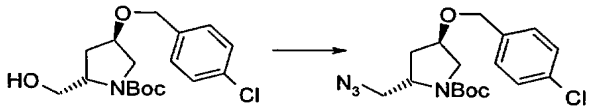
25A. 4-(R)-(4-Chlorobenzyloxy)-2-(S)-hydroxymethylpyrrolidine-1-carboxylic acid *tert*-butyl ester



To a solution of the alcohol shown above (2.00 g, 8.154 mmol) in DMF (41 ml) at 0 °C was added NaH (359 mg of a 60% dispersion in mineral oil, 8.970 mmol) in portions. After 1 h, 4-chlorobenzyl bromide (1.840 g, 8.970 mmol) was added and the mixture warmed to rt. After 15 h, water (300 ml) was added and the aqueous layer extracted with diethyl ether (3 x 50 ml). Organic layers were combined, dried ($MgSO_4$), concentrated and the crude purified by silica column chromatography (40% EtOAc/pet ether) to give the desired ester as an impure oil (1.805 g).

The crude ester obtained above (1.805 g) was dissolved in THF (70 ml) at 0 °C and $LiAlH_4$ (5.00 ml of a 1 M sol in THF, 5.00 mmol) added. After 30 min, water (200 µl) was added dropwise, followed by 10% NaOH (200 µl). After 1 h water (600 µl) was added and the resulting white precipitate filtered off. Concentration of the filtrate and purification of the resulting crude by silica column chromatography (diethyl ether) gave the desired product as an oil (1.232 g, 44% over 2 steps). ^{1}H NMR ($CDCl_3$) δ 1.50 (9H, s), 1.6-2.3 (2H, m), 3.40-4.20 (6H, m), 4.45-4.55 (2H, m), 4.7-4.9 (1H, m), 7.25-7.36 (4H, m).

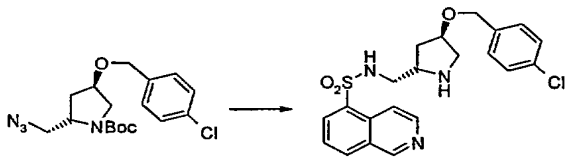
25B. 2-(S)-Azidomethyl-4-(R)-(4-chlorobenzyloxy)pyrrolidine-1-carboxylic acid *tert*-butyl ester



To a solution of the alcohol shown above (425 mg, 1.243 mmol) in DCM (4 ml) at 0 °C was added triethylamine (520 µl, 3.730 mmol). Methanesulphonic anhydride (932 µl of a 2 M sol in DCM, 1.865 mmol) was added dropwise and the resulting solution stirred for 15 min. DCM (10 ml) was added and the organic layer washed with 1 M HCl (10 ml), saturated $NaHCO_3$ (10 ml) and brine (10 ml). The organic layer was dried ($MgSO_4$) and concentrated to give the desired mesylate product as an oil (483 mg), which was used immediately.

The mesylate (483 mg) was dissolved in DMF (6 ml) and sodium azide added (162 mg, 2.486 mmol). After heating to 80 °C for 3 h, the solution was cooled, water (30 ml) added and extracted with EtOAc (30 ml). The organic layer was washed with brine (30ml), dried ($MgSO_4$) and concentrated to give the desired product as an oil (400 mg, 88% over 2 steps). ^1H NMR ($CDCl_3$) δ 1.50 (9H, s), 3.2-4.2 (8H, m), 4.50 (2H, br s), 7.25-7.37 (4H, m).

25C. Isoquinoline-5-sulphonic acid [4-(R)-(4-chlorobenzyloxy)pyrrolidin-2-(S)-ylmethyl]amide



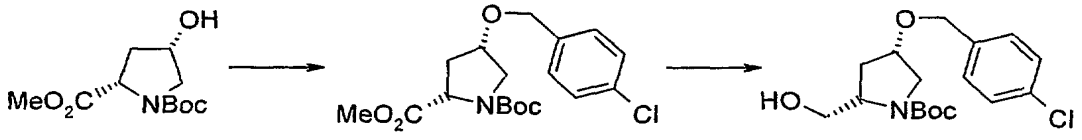
A solution of the azide of Example 25B (50 mg, 0.1363 mmol) in EtOAc (3 ml) with 10% Pd/C (10 mg) was hydrogenated at rt under atmospheric pressure for 2 h. The solution was filtered, concentrated and purified by SCX-2 Isolute column (washing with MeOH, then 1 M NH_3 in MeOH) to give the desired amine intermediate (not shown) as an oil (27 mg) which was used immediately.

To a solution of the amine (27 mg, 0.0792 mmol) in DCM (1 ml) at 0 °C was added triethylamine (55 µl, 0.396 mmol). Isoquinoline-5-sulphonyl chloride hydrochloride (21 mg, 0.0792 mmol) was added in one portion and the resulting solution warmed to rt and stirred for 20 h. The reaction mixture was then concentrated, dissolved in MeOH (1 ml) and 1 M HCl in diethyl ether (2 ml) added. After stirring for 3.5 h, the mixture was concentrated and purified by SCX-2 Isolute column (washing with MeOH, then 1 M NH_3 in MeOH) to give the desired product as an oil (31 mg, 53% over 3 steps). ^{1}H NMR ($CDCl_3$) δ 1.44-1.52 (1H, m), 1.92-2.06 (1H, m), 2.67-2.75 (2H, m), 2.88-3.05 (2H, m), 3.45-3.52 (1H, m), 3.98-4.03 (1H, m), 4.37 (2H, s), 7.13-7.35 (4H, m), 7.67-7.74 (1H, m), 8.17-8.23 (1H, m), 8.43-8.46 (2H, m), 8.69-8.73 (1H, m), 9.37 (1H, d). LC/MS: R_t 4.87 $[M+H]^+$ 432.

EXAMPLE 26

Isoquinoline-5-sulphonic acid [4-(S)-(benzyloxy)pyrrolidin-2-(S)-ylmethyl]amide and Isoquinoline-5-sulphonic acid [4-(S)-(4-chlorobenzyloxy)pyrrolidin-2-(S)-ylmethyl]amide

26A. 4-(S)-(4-Chlorobenzyloxy)-2-(S)-hydroxymethylpyrrolidine-1-carboxylic acid *tert*-butyl ester

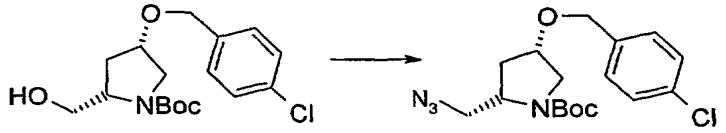


To a solution of the alcohol shown above (1.874 g, 7.640 mmol) in DMF (76 ml) at 0 °C was added NaH (336 mg of a 60% dispersion in mineral oil, 8.404 mmol) in portions. After 1 h, 4-chlorobenzyl bromide (1.727 g, 8.404 mmol) was added and the mixture warmed to rt. After 15 h, water (300 ml) was added and the aqueous layer extracted with diethyl ether (3 x 50 ml). Organic layers were combined, dried ($MgSO_4$), concentrated and the crude purified by silica column chromatography (diethyl ether) to give the desired product as an oil (1.381 g, 49%).

The ester obtained above (1.315 g, 3.556 mmol) was dissolved in diethyl ether (50 ml) at 0 °C and added via cannula to $LiAlH_4$ (135 mg, 3.556 mmol) in a flask at 0

°C. After 30 min, water (135 µl) was added dropwise, followed by 10% NaOH (135 µl). After 1 h water (405 µl) was added and the resulting white precipitate filtered off. Concentration of the filtrate and purification of the resulting crude by silica column chromatography (diethyl ether) gave the desired product as an oil (902 mg, 74%).^{1}H NMR ($CDCl_3$) δ 1.50 (9H, s), 1.7-2.3 (2H, m), 3.40-4.20 (6H, m), 4.50 (2H, br s), 7.26-7.37 (4H, m). LC/MS: R_t 7.56 $[M+H-Boc]^+$ 242.

26B. 2-(S)-Azidomethyl-4-(S)-(4-chlorobenzyloxy)pyrrolidine-1-carboxylic acid *tert*-butyl ester



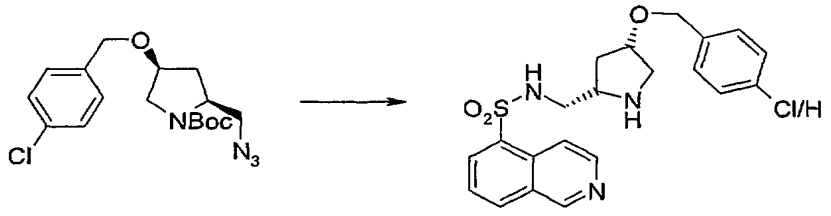
To a solution of the alcohol from Example 26A (824 mg, 2.411 mmol) in DCM (8 ml) at 0 °C was added triethylamine (1.008 ml, 7.232 mmol). Methanesulphonic anhydride (1.808 ml of a 2 M sol in DCM, 3.617 mmol) was added dropwise and the resulting solution stirred for 15 min. DCM (20 ml) was added and the organic layer washed with 1 M HCl (20 ml), saturated $NaHCO_3$ (20 ml) and brine (20 ml). The organic layer was dried ($MgSO_4$) and concentrated to give the desired mesylate product (not shown) as an oil (1.054 g), which was used immediately

The mesylate (1.054 g) was dissolved in DMF (12 ml) and sodium azide (313 mg, 4.822 mmol) added. After heating at 80 °C for 16 h, the solution was cooled, water (70 ml) added and extracted with diethyl ether (30 ml). The organic layer was washed with brine (30 ml), dried ($MgSO_4$), filtered through a plug of silica and concentrated to give the desired product as an oil (619 mg, 70% over 2 steps). ^{1}H NMR ($CDCl_3$) δ 1.50 (9H, s), 2.08-2.23 (2H, m), 3.35-4.20 (6H, m), 4.49 (2H, br s), 7.26-7.37 (4H, m).

26C. Isoquinoline-5-sulphonic acid [4-(S)-(benzyloxy)pyrrolidin-2-(S)-ylmethyl]amide

and

26D. Isoquinoline-5-sulphonic acid [4-(S)-(4-chlorobenzyloxy)pyrrolidin-2-(S)-ylmethyl]amide



A solution of the azide shown above (109 mg, 0.297 mmol) in EtOAc (6 ml) with 10% Pd/C (20 mg) was hydrogenated at rt under atmospheric pressure for 2 h to give the corresponding amine. The solution was filtered and concentrated to give the product as an oil (101 mg), which was used immediately.

To a solution of the amine (101 mg) in DCM (3 ml) at 0 °C was added triethylamine (207 µl, 1.485 mmol). Isoquinoline-5-sulphonyl chloride hydrochloride (79 mg, 0.297 mmol) was added in one portion and the resulting solution warmed to rt and stirred for 18 h. The reaction mixture was then concentrated, dissolved in MeOH (3 ml) and 1 M HCl in diethyl ether (6 ml) added. After stirring for 3.5 h, the mixture was concentrated and purified by NH_2 Isolute column, SCX-2 Isolute column (washing with MeOH, then 1 M NH_3 in MeOH) and silica column chromatography (15% MeOH in DCM) to give a product as a mixture of 4-chlorobenzyl and benzyl ethers (74 mg). A portion of the mixture (24 mg) was separated by preparative HPLC to give the benzyl ether (13 mg) and 4-chlorobenzyl ether (8 mg).

26C:- Benzyl ether; ^{1}H NMR ($CDCl_3$) δ 1.84-1.88 (1H, m), 2.26-2.38 (1H, m), 3.15-3.22 (1H, m), 3.33-3.45 (2H, m), 3.62-3.67 (1H, m), 4.05-4.12 (1H, m), 4.26 (1H, br s), 4.45 (1H, d), 4.56 (1H, d), 7.25-7.38 (4H, m), 7.61-7.68 (1H, m), 8.16-8.20 (1H, m), 8.35-8.38 (1H, m), 8.48-8.50 (1H, m), 8.63-8.66 (1H, m), 9.34 (1H, s). LC/MS: R_t 4.45 $[M+H]^+$ 398.

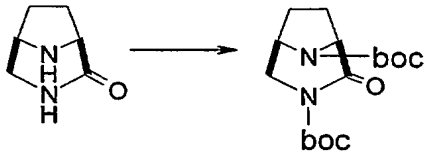
26D:- 4-Chlorobenzyl ether; ^{1}H NMR ($CDCl_3$) δ1.83-1.89 (1H, m), 2.26-2.38 (1H, m), 3.16-3.20 (1H, m), 3.32-3.41 (2H, m), 3.61-3.66 (1H, m), 3.95-4.15 (1H, m),

4.25 (1H, br s), 4.40 (1H, d), 4.53 (1H, d), 7.21-7.30 (4H, m), 7.63-7.69 (1H, m), 8.18-8.21 (1H, m), 8.34-8.37 (1H, m), 8.47-8.50 (1H, m), 8.64-8.68 (1H, m), 9.36 (1H, s). LC/MS: R_t 4.94 $[M+H]^+$ 432.

EXAMPLE 27

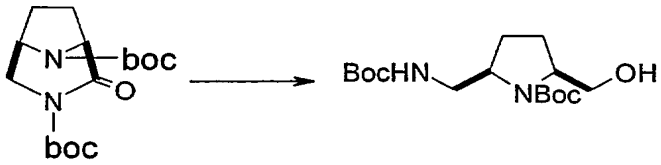
Isoquinoline-5-sulphonic acid [*cis*-5-(4-chlorobenzyloxymethyl)pyrrolidin-2-ylmethyl]amide

27A. 2-Oxo-3,8-diazabicyclo[3.2.1]octane-3,8-dicarboxylic acid di-*tert*-butyl ester



To a solution of the amide shown above (626 mg, 4.962 mmol) in DCM (20 ml) at rt was added triethylamine (3.5 ml, 24.81 mmol), DMAP (303 mg, 2.481 mmol) and di-*tert*-butyl dicarbonate (3.25 g, 14.886 mmol). After stirring for 15 h the mixture was pre-absorbed onto silica and purified by silica column chromatography (50%-80% diethyl ether in hexanes) to give the desired Boc-protected product as an oil (692 mg, 43%).^{1}H NMR ($CDCl_3$) δ 1.48 (9H, s), 1.54 (9H, s), 1.72-1.83 (1H, m), 2.05-2.23 (3H, m), 3.43 (1H, dd), 3.87 (1H, dd), 4.56 (2H, br s).

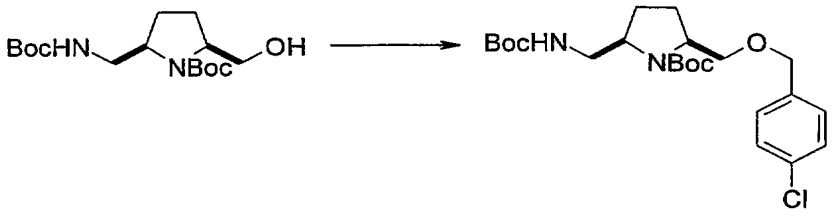
27B. *cis*-2-(*tert*-Butoxycarbonylaminomethyl)-5-hydroxymethylpyrrolidine-1-carboxylic acid *tert*-butyl ester



To a solution of the Boc-protected amide shown above (327 mg, 1.002 mmol) in MeOH (10 ml) at 0 °C was added $NaBH_4$ (76 mg, 2.004 mmol) in one portion. After 1 h, water (20 ml) was added and the aqueous phase extracted with diethyl ether (3 x 20 ml). Organic phases were dried ($MgSO_4$) and concentrated to give the

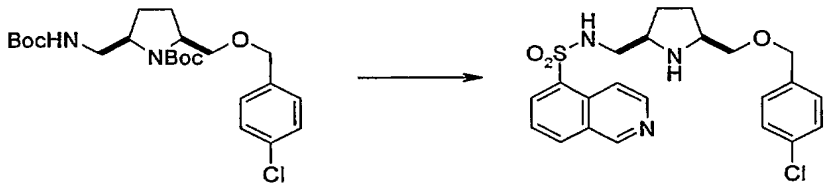
desired product as an oil (331 mg, 100%).^{1}H NMR ($CDCl_3$) δ 1.36 (9H, s), 1.42 (9H, s), 1.6-2.0 (4H, m), 2.9-4.0 (6H, m).

27C. *cis*-2-(*tert*-Butoxycarbonylaminomethyl)-5-(4-chlorobenzyloxymethyl)pyrrolidine-1-carboxylic acid *tert*-butyl ester



To a solution of the alcohol shown above (205 mg, 0.620 mmol) in DMF (5 ml) at 0 °C was added NaH (27 mg of a 60% dispersion in mineral oil, 0.682 mmol) in one portion. After 1 h, 4-chlorobenzyl bromide (134 mg, 0.651 mmol) was added and the mixture warmed rt. After 15 h, water (40 ml) was added and the aqueous layer extracted with diethyl ether (2 x 40 ml). Organic layers were combined, dried (Na_2SO_4), concentrated and the crude purified by silica column chromatography (50-100% EtOAc in hexanes) to give the desired product as an oil (200 mg, 71%). ^{1}H NMR ($CDCl_3$) δ 1.35 (18H, s), 1.6-2.0 (4H, m), 3.07-3.42 (4H, m), 3.87 (2H, br s), 4.36-4.51 (2H, m), 7.16-7.26 (4H, m).

27D. Isoquinoline-5-sulphonic acid [*cis*-5-(4-chlorobenzyloxymethyl)pyrrolidin-2-ylmethyl]amide

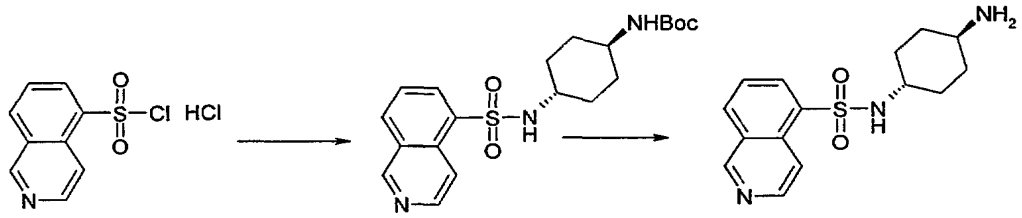


To a solution of the ether shown above (116 mg, 0.255 mmol) in MeOH (3 ml) at rt was added 1 M HCl in diethyl ether (3 ml). After stirring for 22 h, the solution was concentrated and purified by SCX-2 Isolute column (washing with MeOH, then 1 M NH_3 in MeOH) to give the desired de-protected amine as an oil (59 mg), which was used immediately.

To a solution of the amine (59 mg, 0.232 mmol) in DCM (2.3 ml) at 0 °C was added triethylamine (161 µl, 1.158 mmol). Isoquinoline-5-sulphonyl chloride hydrochloride (61 mg, 0.232 mmol) was added in one portion and the resulting solution warmed to rt and stirred for 20 h. The reaction mixture was concentrated, and then purified by NH_2 Isolute column and silica column chromatography (10% MeOH in DCM) to give the desired product as an oil (45 mg, 40% over 2 steps). ^1H NMR ($CDCl_3$) δ 1.42-1.86 (4H, m), 2.76 (2H, d), 3.41-3.54 (2H, m), 3.69-3.79 (1H, m), 3.85-3.94 (1H, m), 4.38 (1H, d), 4.43 (1H, d), 7.12-7.27 (4H, m), 7.60-7.66 (1H, m), 8.12-8.16 (1H, m), 8.35-8.38 (1H, m), 8.60-8.62 (2H, m), 9.27 (1H, s). LC/MS: R_t 5.30 $[M+H]^+$ 446.

EXAMPLE 28

Isoquinoline-5-sulphonic acid (*trans*-4-amino-cyclohexyl)-amide



28A. Preparation of the (*trans*-4-amino-cyclohexyl)-carbamic acid *tert*-butyl ester

In a 100 ml round-bottom flask, under N_2, was placed *trans*-1,4-diaminocyclohexane (1 g, 8.7 mmol) and chloroform (20 ml). A solution of di-*tert*-butyl dicarbonate (0.96 g, 4.4 mmol) in chloroform (15 ml) was added to previous solution over a period of 2h. The milky white suspension was stirred overnight. The chloroform was then removed under reduce pressure. To the obtained white residue was added dichloromethane (15 ml) and a saturated aqueous solution of sodium carbonate (20 ml). The layers were separated and the organic layer was washed twice (10 ml) with the sodium carbonate solution. The dichloromethane solution was collected, dried (MgSO4) and concentrated *in vacuo* to afford a white solid of the required compound. This compound was used in the next step without further purification. (*J Org Chem*, **1996**, *61*, 8815).

Characterising Data:

($C_{10}H_{22}N_2O_2$): ^{1}H NMR ($CDCl_3$, 250 MHz) δ 1.17-1.25 (*m*, 4H), 1.42 (*m*, 2H), 1.44 (*s*, 9H), 1.87 (*m*, 2H), 2.02-2.04 (*m*, 2H), 2.66 (*m*, 1H), 3.42 (*bs*, 1H), 4.39 (*bs*, 1H).

28B. *Trans*-4-(Isoquinoline-5-sulphonylamino)- cyclohexyl]-carbamic acid tert-butyl ester

To a solution of (*trans*-4-amino-cyclohexyl)-carbamic acid tert-butyl ester (197 mg, 0.93 mmol) and triethylamine (0.45 ml, 3 mmol) in dichloromethane (15 ml) was added in small portions the isoquinolin-5-ylsulphonyl chloride hydrochloride (232 mg, 1 mmol) with stirring and cooling on ice. Water (30 ml) was added to the reaction mixture after stirring overnight. The organic layer was then separated and washed twice with water, dried ($MgSO_4$) and concentrated *in vacuo*. The obtained crude was purified by silica flash column chromatography eluting with 10% methanol in dichloromethane to afford the Boc protected compound as a white solid (68 mg, 0.17 mmol, 18%).

Characterising Data:

($C_{20}H_{27}N_3O_4S$): MS (ESI) *m/z* 406.22 [$(M+H)^+$]; ^{1}H NMR ($CDCl_3$, 250 MHz) δ 0.96-1.27 (*m*, 2H), 1.39 (*s*, 9H), 1.71-1.92 (*m*, 4H), 3.09-3.33 (*m*, 3H), 4.30 (*m*, 2H), 5.07 (*m*, 1H), 7.70 (*t*, J = 8 Hz, 1H), 8.21 (*d*, J = 7 Hz, 1H), 8.38 (*d*, J = 6 Hz, 1H), 8.46 (*dd*, J = 7 Hz and J = 1 Hz, 1H), 8.68 (*d*, J = 6 Hz, 1H), 9.36 (*s*, 1H).

28C. Isoquinoline-5-sulphonic acid *(trans*-4-amino-cyclohexyl)-amide

Trifluoroacetic acid (1ml) was added drop wise to a solution of [trans-4-(Isoquinoline-5-sulphonylamino)-cyclohexyl]-carbamic acid tert-butyl ester (68 mg, 0.17 mmol) in dichloromethane (1 ml), with stirring and cooling on ice. After 3h of reaction time the solvents were concentrated *in vacuo* and the obtained crude was purified with a flash NH_2 column (2 g, 15 ml) eluting with methanol to afford the required compound (40 mg, 0.13 mmol, 77%).

Characterising Data:

($C_{15}H_{19}N_3O_2S$): MS (ESI) *m/z* 306.14 [$(M+H)^+$]; ^{1}H NMR (CD_3OD, 250 MHz) δ 0.94-1.91 (*m*, 8H), 2.52-2.61 (*m*, 1H), 3.01-3.07 (*m*, 1H), 7.84 (*t*, *J* = 8 Hz, 1H), 8.42 (*d*, *J* = 8 Hz, 1H), 8.52 (*d*, *J* = 8 Hz, 1H), 8.57 (*d*, *J* = 5 Hz, 1H), 8.64(*d*, *J* = 8 Hz, 1H), 9.42 (*s*, 1H).

BIOLOGICAL ACTIVITY

EXAMPLE 29

Measurement of PKA Kinase Inhibitory Activity (IC_{50})

Compounds of the invention can be tested for PK inhibitory activity using the PKA catalytic domain from Upstate Biotechnology (#14-440) and the 9 residue PKA specific peptide (GRTGRRNSI), also from Upstate Biotechnology (#12-257), as the substrate. A final concentration of 1nM enzyme is used in a buffer that includes 20mM MOPS pH7.2, 40uM ATP/γ^{33}P-ATP and 50mM substrate. Compounds are added in dimethylsulphoxide (DMSO) solution to a final DMSO concentration of 2.5%. The reaction is allowed to proceed for 20 minutes before addition of excess orthophosphoric acid to quench activity. Unincorporated γ^{33}P-ATP is then separated from phosphorylated proteins on a Millipore MAPH filter plate. The plates are washed, scintillant is added and the plates are then subjected to counting on a Packard Topcount.

The % inhibition of the PKa activity is calculated and plotted in order to determine the concentration of test compound required to inhibit 50% of the PKA activity (IC_{50}).

The compounds of Examples 1, 2, 3, 4, 17, 19, 20, 24, 20, 24, 25, 26D and 28 have IC_{50} values of less than 10μM.

EXAMPLE 29

Measurement of PKB Kinase Inhibitory Activity (IC_{50})

The inhibition of protein kinase B (PKB) activity by compounds can be determined determined essentially as described by Andjelkovic *et al.* (Mol. Cell. Biol. 19, 5061-5072 (1999)) but using a fusion protein described as PKB-PIF and described

in full by Yang et al (Nature Structural Biology 9, 940 – 944 (2002)). The protein is purified and activated with PDK1 as described by Yang *et al.* The peptide AKTide-2T (H-A-R-K-R-E-R-T-Y-S-F-G-H-H-A-OH) obtained from Calbiochem (#123900) is used as a substrate. A final concentration of 0.6nM enzyme is used in a buffer that includes 20mM MOPS pH7.2, 30uM ATP/γ^{33}P-ATP and 25μM substrate. Compounds are added in DMSO solution to a final DMSO concentration of 2.5%. The reaction is allowed to proceed for 20 minutes before addition of excess orthophosphoric acid to quench activity. The reaction mixture is transferred to a phosphocellulose filter plate where the peptide binds and the unused ATP is washed away. After washing, scintillant is added and the incorporated activity measured by scintillation counting.

The % inhibition of the PKa activity is calculated and plotted in order to determine the concentration of test compound required to inhibit 50% of the PKB activity (IC_{50}).

Following the protocol described above, the IC_{50} values of the compounds of Examples 1, 2, 3, 4, 5, 6, 7, 9, 10, 11, 12, 14, 15, 17, 19, 23, 24, 25, 26C, 26D, 27 and 28 have been found to be less than 10 μM whilst the compounds of Examples 8, 13, 16, 18, 20, 21 and 22 have IC_{50} values of less than 100 μM.

PHARMACEUTICAL FORMULATIONS

EXAMPLE 30

(i) Tablet Formulation

A tablet composition containing a compound of the formula (I) is prepared by mixing 50mg of the compound with 197mg of lactose (BP) as diluent, and 3mg magnesium stearate as a lubricant and compressing to form a tablet in known manner.

(ii) Capsule Formulation

A capsule formulation is prepared by mixing 100mg of a compound of the formula (I) with 100mg lactose and filling the resulting mixture into standard opaque hard gelatin capsules.

(iii) Injectable Formulation I

A parenteral composition for administration by injection can be prepared by dissolving a compound of the formula (I) (e.g. in a salt form) in water containing 10% propylene glycol to give a concentration of active compound of 1.5 % by weight. The solution is then sterilised by filtration, filled into an ampoule and sealed.

(iv) Injectable Formulation II

A parenteral compositon for injection is prepared by dissolving in water a compound of the formula (I) (e.g. in salt form) (2 mg/ml) and mannitol (50 mg/ml), sterile filtering the solution and filling into sealable 1 ml vials or ampoules.

(iv) Subcutaneous Injection Formulation

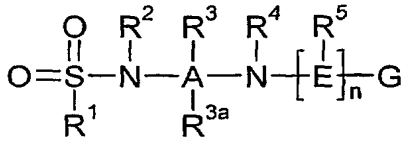
A composition for sub-cutaneous administration is prepared by mixing a compound of the formula (I) with pharmaceutical grade corn oil to give a concentration of 5 mg/ml. The composition is sterilised and filled into a suitable container.

Equivalents

The foregoing examples are presented for the purpose of illustrating the invention and should not be construed as imposing any limitation on the scope of the invention. It will readily be apparent that numerous modifications and alterations may be made to the specific embodiments of the invention described above and illustrated in the examples without departing from the principles underlying the invention. All such modifications and alterations are intended to be embraced by this application.

CLAIMS

1. The use of a compound for the prophylaxis or treatment of a disease state or condition mediated by protein kinase B, the compound having the formula (I^0).



(I^0)

or a salt or solvate thereof;

wherein

n is 0 or 1;

A and E are the same or different and each is an alkylene group of 2 or 3 carbon atoms in length optionally substituted by one or more groups selected from R^{11} and –X-CH(R^6)(R^7);

G is hydrogen when n is 0 and, when n is 1, G is hydrogen or a group –X-CH(R^6)(R^7);

R^1 is an aryl or heteroaryl group having from 5 to 12 ring members;

R^2 and R^4 are the same or different and are each selected from hydrogen, R^7, R^{11} and CH(R^6)(R^7);

R^3, R^{3a} and R^5 are the same or different and are each selected from hydrogen, a group R^{11} and a group –X-CH(R^6)(R^7);

or any one pair or any two non-overlapping pairs selected from R^2 and R^3; R^3 and R^4; R^2 and R^5; R^3 and R^5; R^4 and R^5; R^3 and R^8; and R^4 and R^8 are linked together in a ring and together form an alkylene chain of 1 to 5 carbon atoms in length which may be optionally substituted by one or more groups selected from R^{11} and –X-CH(R^6)(R^7);

or the pair R^2 and R^4 are linked together in a ring and together form an alkylene chain of 2 to 5 carbon atoms in length which may be optionally substituted by one or more groups selected from R^{11} and –X-CH(R^6)(R^7);

and optionally R^3 and R^{3a} may be linked together in a ring and together form an alkylene chain of 1 to 6 carbon atoms in length which may

be optionally substituted by one or more groups selected from R^{11} and –X-$CH(R^6)(R^7)$;

X is selected from O, S, SO, SO_2 and NR^8;

R^6 and R^7 are the same or different and each is selected from hydrogen, saturated C_{1-6} hydrocarbyl, trifluoromethyl, cyano; $CONR^9R^{10}$ and aryl and heteroaryl groups having from 5 to 12 ring members; or R^6 and R^7 together with the carbon atom to which they are attached form a carbocyclic or heterocyclic group having from 5 to 12 ring members;

R^8 is selected from hydrogen, C_{1-4} hydrocarbyl, C_{1-4} acyl, C_{1-4} hydrocarbylsulphonyl;

R^9 and R^{10} are the same or different and each is selected from hydrogen and C_{1-4} hydrocarbyl; and

R^{11} is saturated C_{1-6} hydrocarbyl optionally substituted by hydroxy or C_{1-4} hydrocarbyloxy;

with the provisos that:

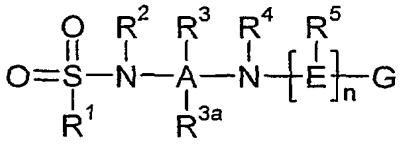
(a) when G is hydrogen and R^1 is a substituted or unsubstituted isoquinoline group, (i) at least one pair selected from R^2 and R^3; R^3 and R^4; R^2 and R^5; R^3 and R^5; and R^4 and R^5 are linked together in a ring; and/or (ii) at least one group –X-$CH(R^6)(R^7)$ is present in the compound; and/or (iii) R^3 and R^{3a} are linked together in a ring;

(b) the compound contains no more than two groups –X-$CH(R^6)(R^7)$; and

(c) when X is O, S or NR^8, a minimum chain length of two carbon atoms is interposed between X and a nitrogen atom of the moiety N-A-N.

2. The use according to claim 1 wherein, when G is hydrogen and R^1 is a substituted or unsubstituted isoquinoline group, (i) at least one pair selected from R^2 and R^3; R^3 and R^4; R^2 and R^5; R^3 and R^5; and R^4 and R^5 are linked together in a ring; and/or (ii) at least one group –X-$CH(R^6)(R^7)$ is present in the compound.

3. A compound of the formula (I):



(I)

or a salt or solvate thereof;

wherein

n is 0 or 1;

A and E are the same or different and each is an alkylene group of 2 or 3 carbon atoms in length optionally substituted by one or more groups selected from R^{11} and –X-CH(R^6)(R^7);

G is hydrogen when n is 0 and, when n is 1, G is hydrogen or a group –X-CH(R^6)(R^7);

R^1 is an aryl or heteroaryl group having from 5 to 12 ring members;

R^2 and R^4 are the same or different and are each selected from hydrogen, R^7, R^{11} and CH(R^6)(R^7);

R^3, R^{3a} and R^5 are the same or different and are each selected from hydrogen, a group R^{11} and a group –X-CH(R^6)(R^7);

or any one pair or any two non-overlapping pairs selected from R^2 and R^3; R^3 and R^4; R^2 and R^5; R^3 and R^5; R^4 and R^5; R^3 and R^8; and R^4 and R^8 are linked together in a ring and together form an alkylene chain of 1 to 5 carbon atoms in length which may be optionally substituted by one or more groups selected from R^{11} and –X-CH(R^6)(R^7);

or the pair R^2 and R^4 are linked together in a ring and together form an alkylene chain of 2 to 5 carbon atoms in length which may be optionally substituted by one or more groups selected from R^{11} and –X-CH(R^6)(R^7);

and optionally R^3 and R^{3a} may be linked together in a ring and together form an alkylene chain of 1 to 6 carbon atoms in length which may be optionally substituted by one or more groups selected from R^{11} and –X-CH(R^6)(R^7);

X is selected from O, S, SO, SO_2 and NR^8;

R^6 and R^7 are the same or different and each is selected from hydrogen, saturated C_{1-6} hydrocarbyl, trifluoromethyl, cyano; $CONR^9R^{10}$

and aryl and heteroaryl groups having from 5 to 12 ring members; or R^6 and R^7 together with the carbon atom to which they are attached form a carbocyclic or heterocyclic group having from 5 to 12 ring members;

R^8 is selected from hydrogen, C_{1-4} hydrocarbyl, C_{1-4} acyl, C_{1-4} hydrocarbylsulphonyl;

R^9 and R^{10} are the same or different and each is selected from hydrogen and C_{1-4} hydrocarbyl; and

R^{11} is saturated C_{1-6} hydrocarbyl optionally substituted by hydroxy or C_{1-4} hydrocarbyloxy;

with the provisos that:

(a) when G is hydrogen and R^1 is a substituted or unsubstituted phenyl, naphthyl or isoquinoline group, (i) at least one pair selected from R^2 and R^3; R^3 and R^4; R^2 and R^5; R^3 and R^5; and R^4 and R^5 are linked together in a ring; and/or (ii) at least one group $-X-CH(R^6)(R^7)$ is present in the compound; and/or (iii) R^3 and R^{3a} are linked together in a ring;

(b) when R^4 and R^8 are linked to form a ring, R^1 is other than an unsubstituted or substituted isoquinoline group;

(c) the compound contains no more than two groups $-X-CH(R^6)(R^7)$; and

(d) when X is O, S or NR^8, a minimum chain length of two carbon atoms is interposed between X and a nitrogen atom of the moiety N-A-N;

and excluding:

(e) compounds where, in combination, G is hydrogen, n is 1, R^4 is hydrogen, R^3 and R^5 combine to form a ring, and no group $-X-CH(R^6)(R^7)$ is present; and

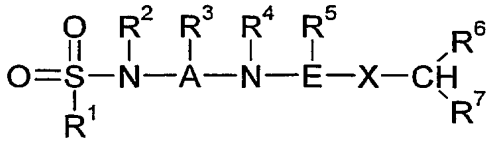
(f) compounds where, in combination, G is hydrogen, n is 0, and R^3 and R^4 combine to form a ring, and no group $-X-CH(R^6)(R^7)$ is present.

4. A compound according to claim 3 wherein, when G is hydrogen and R^1 is a substituted or unsubstituted phenyl, naphthyl or isoquinoline group, (i) at least one pair selected from R^2 and R^3; R^3 and R^4; R^2 and R^5; R^3 and R^5; and

R^4 and R^5 are linked together in a ring; and/or (ii) at least one group –X-$CH(R^6)(R^7)$ is present in the compound.

5. A compound of the formula (I) as defined in claim 3 or claim 4 wherein at least one group –X-$CH(R^6)(R^7)$ is present.

6. A compound according to claim 5 of the of the formula (II):



(II)

or a salt or solvate thereof;
wherein R^1, R^2, R^3, R^4, R^5, X, R^6 and R^7 are as defined in any one of the preceding claims.

7. A compound according to any one of claims 3 to 6 which contains no more than one group –X-$CH(R^6)(R^7)$.

8. A compound according to any one of the preceding claims wherein no more than 3 substituent groups R^{11} are present on any one of A and E.

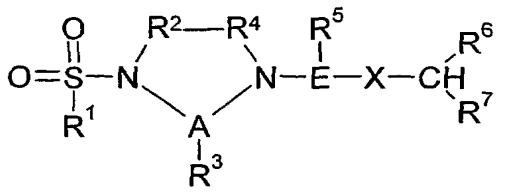
9. A compound according to claim 8 wherein no more than 2 substituent groups R^{11} are present on any one of A and E.

10. A compound according to claim 9 wherein no substituents R^{11} are present on A or E.

11. A compound according to claim 10 wherein A-R^3 takes the form –CH_2-CH_2- or –CH_2-CH_2-CH_2-.

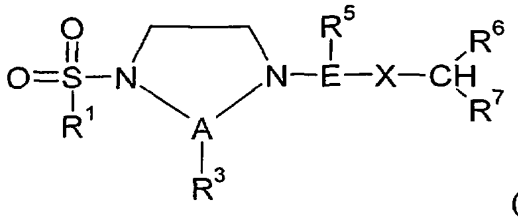
12. A compound according to claim 10 or claim 11 wherein E-R^5 takes the form –CH_2-CH_2- or –CH_2-CH_2-CH_2-.

13. A compound according to any one of claims 3 to 12 having the formula (III):



(III)

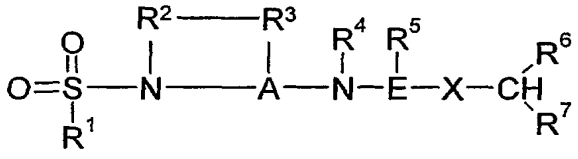
14. A compound according to claim 13 having the formula (IIIa):



(IIIa)

15. A compound according to claim 14 wherein R^3 and R^5 are hydrogen.

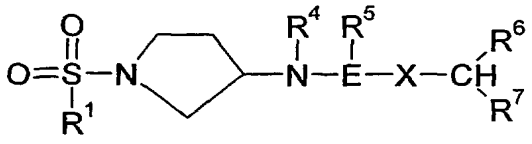
16. A compound according to any one of claims 3 to 12 having the formula (IV):



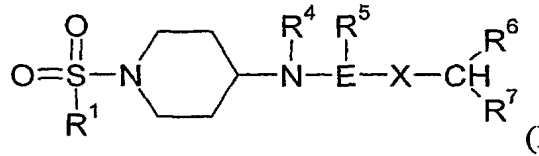
(IV)

17. A compound according to claim 16 wherein R^4 and R^5 are hydrogen.

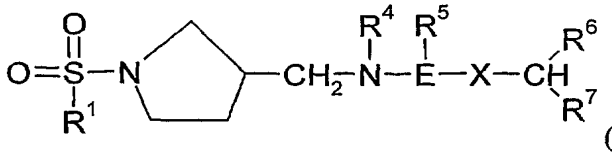
18. A compound according to claim 17 having a formula selected from (IVa), (IVb), (IVc) and (IVd):



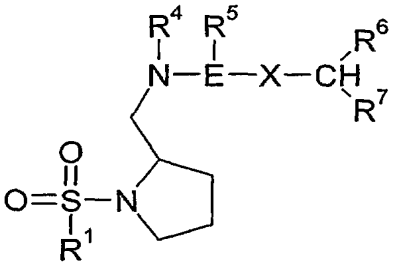
(IVa)



(IVb)

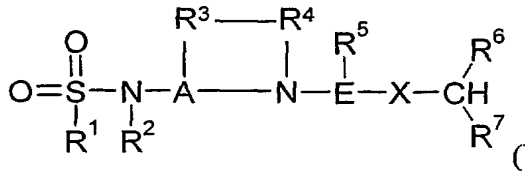


(IVc)



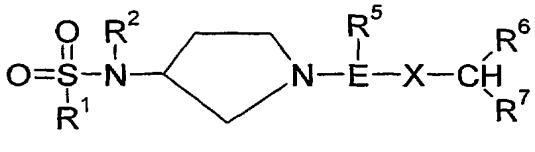
(IVd)

19. A compound according to any one of claims 3 to 10 having the formula:

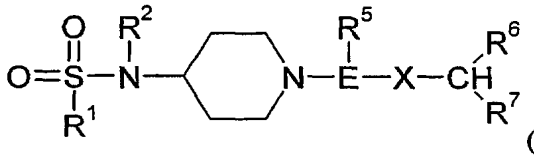


(V)

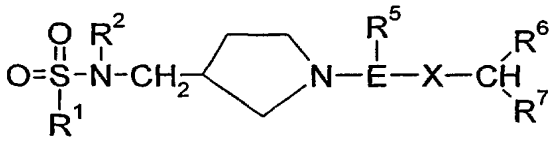
20. A compound according to claim 19 having a formula selected from (Va), (Vb) and (Vc):



(Va)



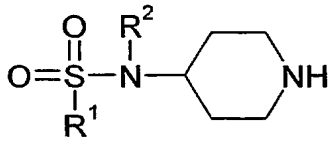
(Vb)



(Vc)

21. A compound according to claim 19 or claim 20 wherein R^2 and R^5 are hydrogen.

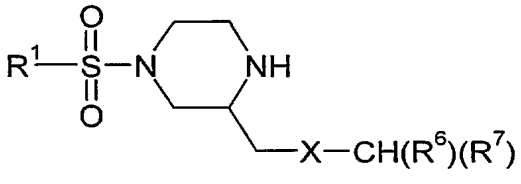
22. A compound according to claim 2 having the formula (Vd):



(Vd)

wherein R^1 and R^2 are as defined in any one of the preceding claims.

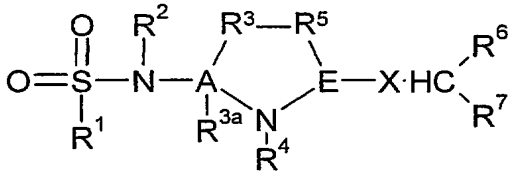
23. A compound according to claim 1 having the formula (Xd):



(Xd)

wherein R1, X, R^6 and R^7 are as defined in any one of the preceding claims.

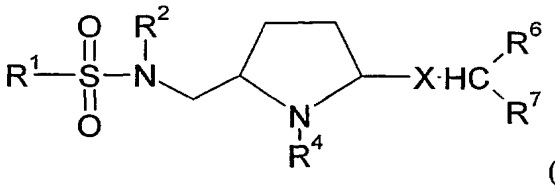
24. A compound according to any one of claims 3 to 10 having the formula (VI)



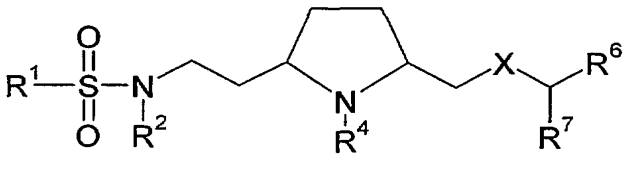
(VI)

25. A compound according to claim 24 wherein the values for R^3, R^5, A and E are such that the resulting ring has from 5 to 7 ring members, more preferably 5 or 6.

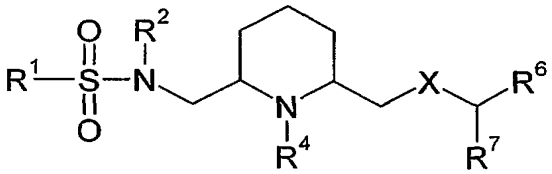
26. A compound according to claim 25 having a formula selected from (VIa), (VIb) and (VIc), and optionally also from (VId), (VIe) and (VIf):



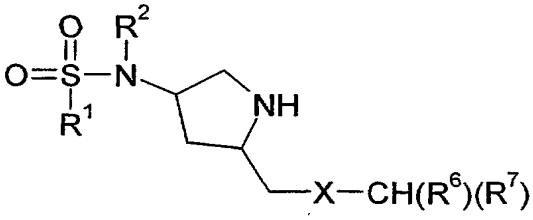
(VIa)



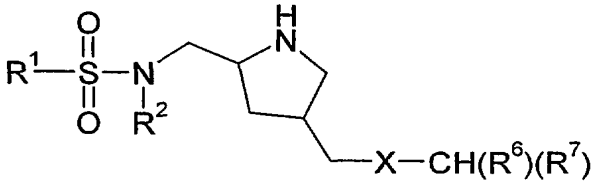
(VIb)



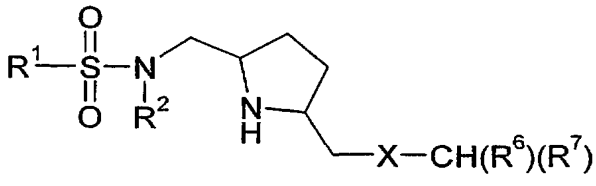
(VIc)



(VId)

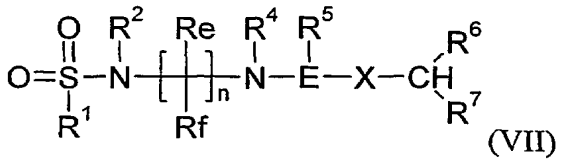


(VIe)



(VIf)

27. A compound according to any one of claims 3 to 12 having the formula (VII):

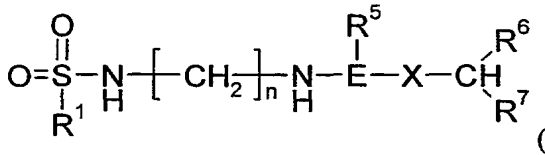


(VII)

wherein R^e and R^f are the same or different and each is selected from hydrogen, R^{11} and –X-CH(R^6)(R^7), and n is 2 or 3.

28. A compound according to claim 27 wherein R^e and R^f are hydrogen.

29. A compound according to claim 28 having the formula (VIIa):



(VIIa)

wherein n is 2 or 3.

30. A compound according to any one of claims 3 to 29 wherein X is O.

31. A compound according to any one of claims 3 to 30 wherein R^1 is a monocyclic or bicyclic group.

32. A compound according to any one of claims 3 to 31 wherein R^1 is heteroaryl.

33. A compound according to any one of claims 3 to 31 wherein R^1 is aryl.

34. A compound according to any one of claims 3 to 33 wherein R^1 has 5 to 10 ring members.

35. A compound according to claim 31 wherein R^1 is selected from optionally substituted phenyl, pyridine, pyrrole, furan, thiophene, imidazole, oxazolyl, oxadiazole, oxatriazole, isoxazole, thiazole, isothiazole, pyrazole, pyrazine, pyrimidine, triazine, triazole, tetrazole, quinoline, isoquinoline, benzfuran, benzthiophene, chroman, thiochroman, benzimidazole, benzoxazole,

benzisoxazole, benzthiazole and benzisothiazole, isobenzofuran, isoindole, indolizine, indoline, isoindoline, purine (e.g., adenine, guanine), indazole, benzodioxole, chromene, isochromene, chroman, isochroman, benzodioxan, quinolizine, benzoxazine, benzodiazine, pyridopyridine, quinoxaline, quinazoline, cinnoline, phthalazine, naphthyridine, pyrrolopyridine, imidazopyridine, pyrrolopyrimidine, pyrazolopyridine, imidazopyrazine, imidazopyridinone, imidazopyrimidinone, isoquinolone, naphthyridinone, pyridine, pyridazinone, pteridine, tetrahydronaphthyl, tetrahydroisoquinolinyl, tetrahydroquinolinyl, dihydrobenzthienyl, dihydrobenzfuranyl, 2,3-dihydroisoindol-1-one, 6,7-dihydropyrrolo[3,4-b]pyrid-5-one, indolinyl and indanyl.

36. A compound according to claim 35 wherein R^1 is selected from optionally substituted phenyl, pyridine, pyrazine, pyrimidine, triazine, quinoline, isoquinoline, isoindole, purine, indazole, quinolizine, benzodiazine, pyridopyridine, quinoxaline, quinazoline, cinnoline, naphthyridine, pyrrolopyridine, imidazopyridine, pyrrolopyrimidine, pyrazolopyridine, imidazopyrazine, imidazopyridinone, imidazopyrimidinone, isoquinolone, naphthyridinone and pyridazinone.

37. A compound according to any one of claims 3 to 36 wherein R^1 is selected from the groups listed in Table 1 herein.

38. A compound according to claim 36 wherein R^1 is selected from optionally substituted isoquinoline, quinoline, quinolizine, quinazoline, cinnoline and naphthyridine.

39. A compound according to claim 06 wherein R^1 is optionally substituted 8isoquinoline, for example, isoquinolin-5-yl.

40. A compound according to any one of claims 3 to 39 wherein R^1 is substituted with one or more substituent groups R^{12} selected from halogen, hydroxy, trifluoromethyl, cyano, nitro, carboxy, amino, carbocyclic and

heterocyclic groups having from 3 to 12 ring members; a group R^a-R^b wherein R^a is a bond, O, CO, $X^1C(X^2)$, $C(X^2)X^1$, $X^1C(X^2)X^1$, S, SO, SO_2, NR^c, SO_2NR^c or NR^cSO_2; and R^b is selected from hydrogen, carbocyclic and heterocyclic groups having from 3 to 7 ring members, and a C_{1-8} hydrocarbyl group optionally substituted by one or more substituents selected from hydroxy, oxo, halogen, cyano, nitro, amino, mono- or di-C_{1-4} hydrocarbylamino, carbocyclic and heterocyclic groups having from 3 to 12 ring members and wherein one or more carbon atoms of the C_{1-8} hydrocarbyl group may optionally be replaced by O, S, SO, SO_2, NR^c, $X^1C(X^2)$, $C(X^2)X^1$ or $X^1C(X^2)X^1$;
R^c is selected from hydrogen and C_{1-4} hydrocarbyl; and
X^1 is O, S or NR^c and X^2 is =O, =S or =NR^c.

41. A compound according to any one of claims 3 to 40 wherein G is hydrogen.

42. A compound according to claim 41 wherein n is 0.

43. A compound according to claim 41 wherein n is 1.

44. A compound according to any one of claims 3 to 40 wherein G is group –X-$CH(R^6)(R^7)$.

45. A compound according to claim 44 wherein at least one of R^6 and R^7 is an aryl or heteroaryl group.

46. A compound according to claim 45 wherein one of R^6 and R^7 is an aryl or heteroaryl group and the other is hydrogen.

47. A compound according to claim 46 wherein R^6 is an optionally substituted phenyl group and R^7 is hydrogen.

48. A compound according to any one of claims 45 to 47 wherein each aryl or heteroaryl group is unsubstituted.

49. A compound according to any one of claims 45 to 47 wherein each aryl or heteroaryl group is substituted by one or more substituent groups R^{12} as defined in claim 38.

50. A compound according to claim 49 wherein the substituent groups are selected from halogen, hydroxy, trifluoromethyl, cyano, carboxy, carbocyclic and heterocyclic groups having from 3 to 12 ring members; a group R^a-R^b wherein R^a is a bond, O, CO, S, SO, SO_2; and R^b is selected from hydrogen, carbocyclic groups having from 3 to 6 ring members, heterocyclic groups having from 4 to 6 ring members, and a C_{1-8} hydrocarbyl group optionally substituted by one or more substituents selected from hydroxy, oxo, fluorine, cyano, amino, mono- or di-C_{1-4} hydrocarbylamino, carbocyclic and heterocyclic groups having from 3 to 12 ring members and wherein one or more carbon atoms of the C_{1-8} hydrocarbyl group may optionally be replaced by O, S, SO, SO_2, NR^c; and R^c is selected from hydrogen and C_{1-4} hydrocarbyl.

51. A compound according to claim 50 wherein the substituent groups are selected from halogen and alkyl.

52. A compound according to any one of claims 3 to 29 and 31 to 51 wherein X is NR^8, and R^8 is selected from hydrogen, C_{1-4} hydrocarbyl, C_{1-4} acyl, and C_{1-4} hydrocarbylsulphonyl.

53. A compound according to any one of the claims 3 to 52 having a molecular weight not exceeding 1000 daltons, preferably of less than 750, for example less than 700, or less than 650, or less than 600, or less than 550 daltons, and more preferably less than 525, for example 500 or less.

54. A compound selected from:

isoquinoline-5-sulphonic acid [2-(2-benzyloxy-ethylamino)-ethyl]-amide;
isoquinoline-5-sulphonic acid {2-[2-(4-chloro-benzyloxy)-ethylamino]-ethyl}-amide;

isoquinoline-5-sulphonic acid {2-[2-(2-chloro-benzyloxy)-ethylamino]-ethyl}-amide;

isoquinoline-5-sulphonic acid {2-[2-(3-chloro-benzyloxy)-ethylamino]-ethyl}-amide;

isoquinoline-5-sulphonic acid {2-[2-(2-methyl-benzyloxy)-ethylamino]-ethyl}-amide;

isoquinoline-5-sulphonic acid {2-[2-(3-methyl-benzyloxy)-ethylamino]-ethyl}-amide;

isoquinoline-5-sulphonic acid {2-[2-(4-methyl-benzyloxy)-ethylamino]-ethyl}-amide;

N-[2-(2-Benzyloxy-ethylamino)-ethyl]-3-nitro-benzenesulphonamide;

isoquinoline-5-sulphonic acid (pyrrolidin-3-yl)-amide;

isoquinoline-5-sulphonic acid (pyrrolidin-2-ylmethyl)-amide;

isoquinoline-5-sulphonic acid {2-[2-(2-methoxy-benzyloxy)-ethylamino]-ethyl}-amide;

isoquinoline-5-sulphonic acid {2-[2-(3-methoxy-benzyloxy)-ethylamino]-ethyl}-amide;

isoquinoline-5-sulphonic acid {2-[2-(4-methoxy-benzyloxy)-ethylamino]-ethyl}-amide;

isoquinoline-5-sulphonic acid {2-[2-(3,4-dichloro-benzyloxy)-ethylamino]-ethyl}-amide;

isoquinoline-5-sulphonic acid {2-[2-(3-nitro-benzyloxy)-ethylamino]-ethyl}-amide;

isoquinoline-5-sulphonic acid {2-[2-(3-acetamido-benzyloxy)-ethylamino]-ethyl}-amide;

isoquinoline-5-sulphonic acid piperidin-4-ylamide;

1-(isoquinoline-5-sulphonyl)-piperidin-4-ylamine;

2-(3,4-dichloro-benzyloxy)-ethyl]-[1-(isoquinoline-5-sulphonyl)-piperidin-4-yl]-amine;

isoquinoline-5-sulphonic acid piperidin-3-ylamide;

5-[3-(4-chloro-benzyloxymethyl)-piperazine-1-sulphonyl]-isoquinoline;

isoquinoline-5-sulphonic acid [5-(S)-(4-chlorobenzyloxymethyl)pyrrolidin-3-(R)-yl]methoxymethyl amide;
isoquinoline-5-sulphonic acid [5-(S)-(4-chlorobenzyloxymethyl)pyrrolidin-3-(R)-yl] amide;
isoquinoline-5-sulphonic acid [5-(S)-(4-chlorobenzyloxymethyl)pyrrolidin-3-(R)-yl] amide;
isoquinoline-5-sulphonic acid [4-(R)-(4-chlorobenzyloxy)pyrrolidin-2-(S)-ylmethyl]amide;
isoquinoline-5-sulphonic acid [4-(S)-(benzyloxy)pyrrolidin-2-(S)-ylmethyl]amide;
isoquinoline-5-sulphonic acid [4-(S)-(4-chlorobenzyloxy)pyrrolidin-2-(S)-ylmethyl]amide;
isoquinoline-5-sulphonic acid [*cis*-5-(4-chlorobenzyloxymethyl)pyrrolidin-2-ylmethyl]amide; and
isoquinoline-5-sulphonic acid (*trans*-4-amino-cyclohexyl)-amide.

55. A compound according to any one of claims 3 to 54 in the form of a salt or solvate (such as a hydrate).

56. A compound as defined in any one of claims 1 to 55 for use in the prophylaxis or treatment of a disease state or condition mediated by protein kinase B.

57. The use of a compound as defined in any one of claims 1 to 55 for the manufacture of a medicament for the prophylaxis or treatment of a disease state or condition mediated by protein kinase B.

58. A method for the prophylaxis or treatment of a disease state or condition mediated by protein kinase B, which method comprises administering to a subject in need thereof a compound as defined in any one of claims 1 to 55.

59. A method for treating a disease or condition comprising or arising from abnormal cell growth in a mammal, which method comprises administering

to the mammal a compound as defined in any one of claims 1 to 55 in an amount effective in inhibiting abnormal cell growth.

60. A method for treating a disease or condition comprising or arising from abnormal cell growth in a mammal, the method comprising administering to the mammal a compound as defined in any one of claims 1 to 55 in an amount effective to inhibit PKB activity.

61. A method of inhibiting a protein kinase B, which method comprises contacting the kinase with a kinase-inhibiting compound as defined in any one of claims 1 to 55.

62. A method of modulating a cellular process by inhibiting the activity of a protein kinase B using a compound as defined in any one of claims 1 to 55.

63. A method for treating an immune disorder in a mammal, the method comprising administering to the mammal a compound as defined in any one of claims 1 to 55 in an amount effective to inhibit PKB activity.

64. A compound as defined in any one of claims 1 to 55 for use in the prophylaxis or treatment of a disease state or condition mediated by protein kinase A.

65. The use of a compound as defined in any one of claims 1 to 55 for the manufacture of a medicament for the prophylaxis or treatment of a disease state or condition mediated by protein kinase A.

66. A method for the prophylaxis or treatment of a disease state or condition mediated by protein kinase A, which method comprises administering to a subject in need thereof a compound as defined in any one of claims 1 to 55.

67. A method for treating a disease or condition comprising or arising from abnormal cell growth in a mammal, the method comprising administering to the mammal a compound as defined in any one of claims 1 to 55 in an amount effective to inhibit PKA.

68. A method of inhibiting a protein kinase A, which method comprises contacting the kinase with a kinase-inhibiting compound as defined in any one of claims 1 to 55.

69. A method of modulating a cellular process by inhibiting the activity of a protein kinase A using a compound as defined in any one of claims 1 to 55.

70. A method for treating an immune disorder in a mammal, the method comprising administering to the mammal a compound as defined in any one of claims 1 to 55 in an amount effective to inhibit PKA activity.

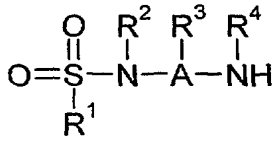
71. A method of inducing apoptosis in a cancer cell, which method comprises contacting the cancer cell with a compound as defined in any one of claims 1 to 55.

72. A pharmaceutical composition comprising a novel compound as defined in any one of claims 1 to 55 and a pharmaceutically acceptable carrier.

73. A compound as defined in any one of claims 1 to 55 for use in medicine.

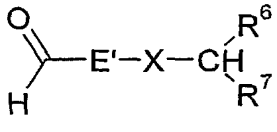
74. A process for the preparation of a compound of the formula (I) as defined in any one of the preceding claims, which process comprises:

(i) the reaction of a compound of the formula (XI):



(XI)

or a protected form thereof, with an aldehyde of the formula(XII):

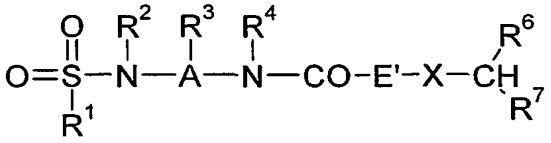


(XII)

or a protected form thereof, wherein E' is an alkylene group of 1 or 2 carbon atoms in length (e.g. a group $(CH_2)_r$ where r is 1 or 2) optionally substituted

by one or more groups selected from R^{11} and –X-CH(R^6)(R^7) where X, R^1 to R^4, R^6, R^7 and R^{11} are as defined in any one of the preceding claims, under reductive amination conditions; or

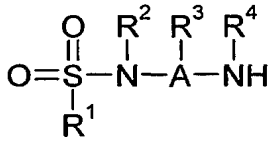
(ii) the reduction of an amide of the formula (XVI):



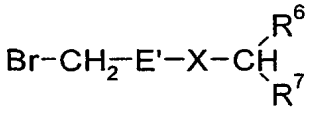
(XVI)

or a protected form thereof, or

(iii) the reaction of an amine of the formula (XI):



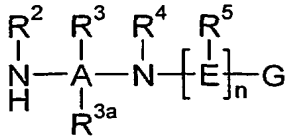
or a protected form thereof, with a bromide of the formula (XVII):



(XVII)

or a protected form thereof, where E', X, R^6 and R^7 are as hereinbefore defined; or

(iv) the reaction of an aromatic or heteroaromatic sulphonyl chloride of the formula R^1SO_2Cl or a protected form thereof, with an amine of the formula (XVIII):



(XVIII)

or a protected form thereof;

and thereafter removing any protecting groups present;

and optionally converting one compound of the formula (I) into another compound of the formula (I).